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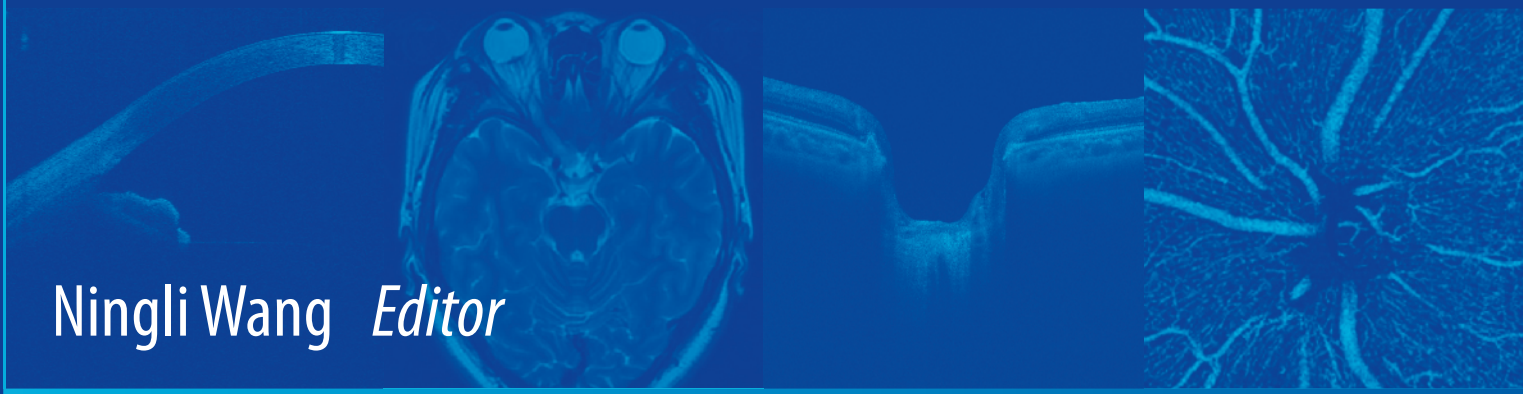
Series Editor: Ningli Wang



Ningli Wang *Editor*

Integrative Ophthalmology

PEOPLE'S MEDICAL PUBLISHING HOUSE

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Advances in Visual Science and Eye Diseases

Series Editor

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Advances in Visual Science and Eye Diseases presents the latest progress and achievement made in visual science and eye diseases for eye care health professionals at different links in the chain of eye care delivery including ophthalmologists, researchers, eye care service providers, health policy makers, and medical students.

The series firstly covers major blinding eye diseases, expounding on their characteristics and the latest development in pathogenesis, up-to-date researches and treatment options of the diseases in detail. Then, the series unfolds the pathogenesis, new diagnosis methods, latest surgery techniques, genetic research, animal modelling studies and translational medicine in glaucoma. Next, the series provides an overall picture on 1. the development of ophthalmology in China along with the contribution of Chinese ophthalmologists to the international community from historical perspective and sheds light on its future development directions; 2. eye epidemiological studies and achievements in blindness prevention in China; 3. holistic view on the systematic relationship between the eye and other organs as well as the relationship between eye diseases and systematic diseases. We hope readers can benefit from this series by enriching their latest knowledge in no matter visual science or clinical management of eye diseases.

Ningli Wang is a professor at Beijing Tongren Hospital affiliated to Capital Medical University, Beijing, China. He is also the director of Tongren Eye Center, Beijing, China.

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ISSN 2524-566X ISSN 2524-5678 (electronic)
Advances in Visual Science and Eye Diseases
ISBN 978-981-13-7895-9 ISBN 978-981-13-7896-6 (eBook)
https://doi.org/10.1007/978-981-13-7896-6

Jointly published with People's Medical Publishing House, PR of China
The print edition is not for sale in China. Customers from China please order the print book from: People's Medical Publishing House, PR of China.

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword 1

It is estimated that, except ocular trauma, only 15% ocular diseases are directly resulted from abnormal ocular structure or function, while the remaining 85% are caused by abnormalities in other organs. If an ophthalmologist only focuses on the eyes in the diagnosis and treatment, it means he is trying to cure all diseases with only 15% of his capability, and the consequences will be devastating.

It is difficult for both ophthalmologists and doctors in other departments to understand this conclusion, since we know so little about the pathogenesis of systemic diseases that can cause eye diseases. There is a famous saying that the eye is the window of the soul. In fact, it is the best organ to reflect the health of the entire body. For example, the pale conjunctiva represents anemia of the blood system; the yellow sclera may reflect liver failure; the change of pupil size may indicate foodborne illness. Paying attention to systemic diseases could be conducive to the prevention and treatment of eye diseases. Understanding the systematic factors resulting in ocular lesions and applying them to the treatment and diagnosis in ophthalmology are what integrative ophthalmology is going to do.

Integrative ophthalmology is an important part of holistic integrative medicine. Although the theory of integrative medicine was proposed just recently, its practice has a long history. At the beginning of the Tang Dynasty, a famous doctor named Simiao Sun found that fine diet may lead to beriberi disease, which can be cured by adding bran to the diet, while rough diet may result in nyctalopia, which could be cured by eating pork liver (I don't know if the idiom "Xing Gan Ming Mu" comes from that). At that time, we didn't know that nyctalopia was a result of vitamin A deficiency. If we figured it out at that time, we would definitely win the Nobel Prize, except that at that time, Mr. Nobel was not born yet! So far, numerous eye diseases still remain incurable or have only imperfect treatment options, and some may even become severer after the treatment. The fact is that we know too little about the pathogenesis of many eye diseases. Ocular diseases may be presentations of the abnormalities of the whole body. To understand the pathogenesis of ocular diseases, there is much we need to learn from Mr. Simiao Sun!

Professor Wang is a distinguished ophthalmologist in China. He has many unique insights and exquisite techniques in the field of ophthalmology. What is more valuable is that he is

committed to connecting ocular diseases with the abnormalities of the whole body. He invited many experts other than ophthalmologists to write this book called *Integrative Ophthalmology*. He is also the first pioneer in this aspect and could be regarded as the founder of integrative ophthalmology. This book is just a beginning. It is the first version of *Integrative Ophthalmology*, so it may not be perfect. We know that it is difficult to perceive everything in the world and even harder to link all the things together. However, it doesn't matter; as long as we insist on writing it year after year, we will ultimately get the ideal version of *Integrative Ophthalmology*.

Xian, China
March 20, 2019

Daiming Fan

Foreword 2

When I received this manuscript titled *Integrative Ophthalmology* from Professor Ningli Wang, I was deeply impressed by his talents and his keen grasp of future development and direction of ophthalmology.

I have known Professor Wang for many years, but it was only after I came to Beijing Tongren Hospital in 2012 that I had a better understanding of his work and had the opportunity to work closely with him. Over the past 2 years, he has made great progress as a manager and as the vice president of the hospital, then the director of the Beijing Institute of Ophthalmology, and the secretary of the party committee of the hospital. He is a famous ophthalmologist in China and also serves as the president of the Chinese Ophthalmological Society and has been awarded the title of Academician Fellow of the Academia Ophthalmologica Internationalis. He is also a successful scholar and has been awarded two National Science and Technology Progress Second Class Awards and published SCI articles with an impact factor of more than 20. There are endless amounts of hard work behind such prestigious achievements of Professor Wang, which is also reflected in his ambition and persistence in academics. In him, I see the success and generosity of a medical practitioner, along with the sagacious perception and wisdom of a scholar.

At the annual meeting of the Chinese Medical Association in January 2013, Professor Wang was fortunate enough to hear an excellent lecture on "Holistic Integrative Medicine" by Academician Daiming Fan and Academician Xuetao Cao. He was deeply inspired and caught a glimpse of the key to breaking the bottleneck in the development of ophthalmology.

After the meeting, he approached Academician Fan, eagerly asking him for advice, exchanging idea, and consulting on the literature for the study. Subsequently, under the guidance of Academician Fan, the "First Integrative Ophthalmology Conference" was held in October 2013. Experts from various clinical departments such as ophthalmology, internal medicine, surgery, neurology, radiology, endocrinology, oncology, and gynecology, as well as professors

in biomedical research, were invited to participate in the conference. For the first time, integrative medicine was used to analyze eye diseases from different perspectives, proving the conference to be a huge success. Following this, in June 2014, the "First Integrative Glaucoma Conference" was organized by the Chinese Ophthalmological Society and the Beijing Ophthalmological Society. This conference further discussed glaucoma with diagnosis and treatment strategies in integrative medicine. After obtaining the agreement of the experts who attended both conferences, Professor Wang decided to invite experts who resonated with his work to participate in and publish their conclusions in a book titled *Integrative Ophthalmology*, which is an academic report as well as an open-minded inquiry that sums up the two academic conferences in about 400,000 words, indicating Professor Wang's keen academic vision and wisdom.

The essence of *Integrative Ophthalmology* is to study the systemic factors that cause eye diseases and apply them to the diagnosis and treatment of eye diseases. It not only is the integration of traditional and modern medicine but also conveys the essence of the profound culture-based traditional medicine in our country.

Furthermore, it is also an integration of ophthalmology and other medical disciplines, as well as a practice that is worthy of reference for other professional disciplines. The book will have a positive impact on the promotion of ophthalmology. In this work, we may understand more of integrative ophthalmology, the philosophies behind such a writing process, and even the makings of a successful scholar or may begin to contemplate the necessary correlation between integrative medicine and other disciplines. If you've set your mind to accomplish something and are willing to pair it with coherent thinking, this book will be a great learning tool for you.

Beijing, China
March 20, 2019

Jixiang Wu

Preface

At the annual meeting of the Chinese Medical Association in January 2013, I had the honor to listen to the wonderful lectures on "Holistic Integrative Medicine" delivered by Academician Daiming Fan and Academician Xuetao Cao. Enlightened by their speeches, I realized the thinking mode of holistic integrative medicine might be the key to breaking the bottleneck in the development of ophthalmology. Therefore, I eagerly consulted Academician Fan right after the meeting and read related literature to gain a better understanding of this concept. Later, under his guidance, we held the "First Integrative Ophthalmology Conference" in October 2013.

At the meeting, Academician Fan illustrated the theory of integrative medicine with clear outline, interspersing with extensive quotations as well as witty remarks, and won applause from all the participants; experts on ophthalmology, internal medicine, surgery, neurology, radiology, endocrinology, oncology, and gynecology; as well as professors in biomedical research. For the first time, ophthalmology was discussed from different perspectives with the thinking mode of integrative medicine. The meeting was a complete success and prompted the Chinese Ophthalmological Society and the Beijing Ophthalmological Society to organize the "First Integrative Glaucoma Conference" in June 2014, which further elaborated the integrated diagnosis and treatment strategies of glaucoma. With the consent of attendees, the book, *Integrative Ophthalmology*, a compilation of discussions presented at the previous two conferences, was finished with the joint effort of our team and those who have passion in promoting the development of integrative ophthalmology.

Through nearly 1 year's exploration, combined with the enlightenment from applying the thinking mode of integrative medicine in digestive and psychiatric departments, we set the definition of "integrative ophthalmology" (IO) as the pathogenesis, treatment, or specific problems of long-term subdivided eye diseases which should be investigated, studied, and analyzed systematically and holistically and should be adjusted and sublimated considering the impact of the society, environment, and mental state, so as to make it a new system more suitable for the treatment of ophthalmology.

The book consists of nine parts. The first part is an introduction, which discusses the definition and thinking mode of integrative medicine and integrative ophthalmology in detail. The

second part, intracranial and intraocular pressure gradient-related diseases, systematically integrates and discusses the diseases related to the brain and eyes. The third part expounds the relationship between eye diseases and the factors associated with life activities such as circadian rhythm, physiopathology, exercise, environment, and mental state. The fourth to ninth parts, respectively, carries out integrative analysis on systemic tumors and eye tumors, cardiovascular disease and eye disease, internal medicine and eye disease, immune system and eye disease, surgery and eye disease, gynecology, obstetrics, and eye disease.

This book is the first of its kind to apply the thinking mode of integrative medicine to ophthalmology, while some parts of this book might not be able to express the essence of integration. We could not pursue perfection in the first time but will do it in continuous enhancement and progress. Therefore, in this book, some parts will be inspiring, while some parts will be inadequate which we hope will be refined in the second and third editions.

The process of improvement and optimization of the book is also the process of popularization and application of integrative ophthalmology. I believe that integrative ophthalmology is the key to the development of ophthalmology.

Beijing, China
March 20, 2019

Ningli Wang

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Part I

Introduction

Holistic Integrative Medicine

1

Daiming Fan and Ningli Wang

Many people engaging in medical science asked me, "You've been working on the exploration of Holistic Integrative Medicine (HIM) for quite a while. What is the progress you have made in your research? Have you got your article published? May I be your first reader?" Each time I was confronted with such a situation, I felt embarrassed and speechless. Just as an old saying goes, it is easy to put the boat along with the current but it is difficult to sail against the current [1].

When an author writes an article, he frequently coins a new term or defines a new concept to guide the reader to grasp its key point, just like following the vine to get the melon. This time it is difficult to define holistic integrative medicine in words even though I have a clear idea in my mind [2].

In terms of "integration," we should discuss the universal laws based on which human knowledge arises and develops. Epistemology holds that knowledge and practice are the two essential means for mankind to gain an insight into the world. Practice is not only the basis of knowledge but also the sole criterion to verify the knowledge. Knowledge may be developed from practice and in turn serves practice. During the process of knowing, people discover the nature laws through practice, and again through practice verify and take advantages of the nature laws. Practice, knowledge, again practice, and again knowledge. This form repeats itself in endless cycles, and with each cycle the content of practice and knowledge rises to a higher level. Unity and diversity of the world determine the people's perception of the world. People know the world either from integrated perspective or from differentiated perspective. As a unity of opposites, differentiation and integration oppose each other and complement each other. Such a law is reflected at every stage of the development of science. Differentiation of science refers to the differentiation of one or several comparatively independent disciplines from one essential discipline. Integration of science refers to the overlapping and merging of similar or even different disciplines, which aims at breaking the boundaries of existing disciplines and establishing many marginal or holistic disciplines so that the irrelevant disciplines are closely integrated into an organic body. HIM means that people conduct an organic integration of the most advanced knowledge and theory in medical sciences and the most valuable clinical experiences to establish a new medical system. It will be beneficial to people's health and is effective in medical treatment by implementing unceasing adjustment in accordance with the changes of society, environment, and patient's psychology [3, 4]. The Chinese character "zheng" (Zen in English) refers to rearrangement which is a strategy focusing on process while the Chinese character "he" refers to fitness which is a standard with the emphasis on result. Therefore, HIM originates from history and philosophy so it should be in conformity with historical trend, scientific laws, and people's will.

The development of the world accords with the phenomenon of "unity after a long time of division and division after a long time of unity," complies with the trend of "spiral development," and abides by the law of "the negation of negation" and "the unity of opposites," which embodies the philosophical concept that "one divides into two" and "two combine into one." With too long or too tight unity, new things will be difficult to emerge and social development will be blocked. With too long or too frequent division, there will be no cohesive force and the motivation of making progress. It is true to nature although no noticeable changes take place in the world

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_1

in a certain period of time (maybe thousands of years). Either division or unity is just what people view things from different perspectives. The essence of the world lies in the law of unity and division. For example, it is self-evident that there are cells and organs in human body and they are indispensable. However, with the explosion of human knowledge, "organ-based theory," "cell-based theory," and even "gene-based theory" were proposed. Just as the rivers join and split, whether we make a division or achieve a unity should comply with the laws of nature, which is "the theory of division and unity" proposed in this chapter.

The development of medicine is a kernel part of scientific advancement in the world and abides by the laws of nature. In the early stage of medical development during the early period of human development, people who were short of practical experience and knowledge explored the unknown areas, such as the mysterious phenomena related to their life and health through primitive social activities and backward productive forces. The dispersed, sporadic, and personal experience was collected and compiled into several books which were passed down from the masters to their apprentices, particularly from father to his sons. Unity is a typical feature of this period, emphasizing the concept that "two combine into one." For example, the rich knowledge of traditional Chinese medicine was compiled into three books:

Huangdi Neijing, which is related to preclinical medicine; Shanghan Zabing Lun, which is concerned with clinical medicine; and Shennong's Herbal, which is associated with pharmacology. Medical development in this period is mainly characterized by integration. The early practice of medical pioneers constructed the tentative framework of traditional Chinese medicine permeated with the concept of "the unity of man and nature," namely, man is an integrated part of nature and vice versa. "Those who submit will prosper, those who resist will perish." Several well-known medical masters such as Bian Que, Hua Tuo, and Zhang Zhongjing accumulated a large amount of medical knowledge through practice. Bian Que, who is said to have lived more than 300 years, wrote two books entitled Bian Que Neijing and Bian Que Waijing. In fact, he did not live to that old age. It is people who attributed 300 years' contributions of medical workers to him, which embodies the concept that "two combine into one" during the early medical development and is somewhat similar to holistic integrative medicine in this chapter or primary integrated medicine.

As time went by, with the accumulation of experience and knowledge and with the increase of more famous doctors who had unique skills, a relatively systematic framework of traditional Chinese medicine was established, which is a valuable knowledge reservoir of Chinese medicine and pharmacology [5]. However, integrated medicine gradually developed into special medical disciplines since Qin Dynasty and was divided into internal medicine, surgery, gynecology, pediatrics, and other disciplines in Han Dynasty and Tang Dynasty. Meanwhile, pharmacology developed with the discovery of more traditional Chinese herbs and their properties and effects. The formulae in the book Thousand Pieces of Gold Formulae were said to have the effect of "treating any diseases." Newly Revised Materia Medica, the first pharmacopoeia in the world, was published in Tang Dynasty.

Both TCM and Western medicine serve the same purpose in two separate ways. Although Western medicine has also developed following the trend of division, its developmental speed and degree are more apparent than TCM. Because Western philosophy and Chinese philosophy have different origins, Western medicine puts more emphasis on evidence-based practice, qualitative study, and quantitative study at the cellular and molecular levels, while TCM takes all factors into consideration and makes a systematic study at the macro-level. Both of them have made great contributions to world medicine [6–8]. (Detailed discussion of this aspect will be omitted for the limited length of this chapter.) However, it should be particularly pointed out that medicine has made a rapid progress from macro-level to microlevel since Antonie van Leeuwenhoek invented a microscope in the seventeenth century and then medicine was divided into preclinical medicine, clinical medicine, and preventive medicine. In preclinical medicine, the structure of human body is divided into different systems, each of which consists of some organs. Each organ is further divided into different tissues composed of cells, organelles, molecules (protein, DNA, and RNA), etc. As for clinical medicine, it is divided into internal medicine, surgery, and medical specialized disciplines and then it is divided into gastroenterology, hematology, cardiology, orthopedics, general surgery, urology, etc., which are called third-tier/level disciplines.

Many third-tier/level disciplines are divided into more specialized ones in recent 10–20 years. I wonder whether they could be called fourth-tier/level disciplines. For instance, orthopedics department consists of several divisions concerning spine, joints, limbs, etc. Gastroenterology department is composed of different divisions for the treatment of gastrointestinal, liver, colorectal, pancreatic diseases, etc. In addition, the former Chinese Society of Gastroenterology has been divided into current Chinese Society of Gastroenterology, Chinese Society of Hepatology, and Chinese Society of Digestive Endoscopy. Accordingly, the former Chinese Journal of Digestion has been divided into today's Chinese Journal of Digestion, Chinese Journal of Hepatology, Chinese Journal of Digestive Endoscopy, and Chinese Journal of Pancreatology. At present, a so-called fourth-tier/level discipline has been divided into many cooperative groups, with the number amounting to more than ten. Furthermore, some people propose that surgery should be further divided into more specialized divisions. I wonder how specialized the division should be. It seems that one will never give up if the whole human body is not broken into pieces, with his head decapi-

tated, his heart and lungs torn up, his spleen and stomach separated, and his liver and intestines cut into inches, which is one of the features of modern medicine.

It is true that the unceasing division has enhanced the development of modern medicine. Nowadays people have had a better understanding of their bodies and have acquired much more medical knowledge, and the medical treatment has become more effective. There is no denying that the therapeutic effect has been enhanced and people's life span has been increased. However, we also admit that division of medicine has brought some disadvantages, detriment, and even disastrous effects, which are reflected in the following nine aspects.

1.1 Patients Are Treated as Organs

With the more specialized division of clinical departments, doctors have a dim impression of general medicine. Compared with the experienced doctors, the green hands have no access to the training of integrated medicine. As a result, they only have a command of medical knowledge concerning the fourth-tier/level disciplines and a part of human body. Consciously or unconsciously, they see their patient as an organ. For example, they treat a patient with liver cancer as a cancerous liver, namely, they pay more attention to carcinoma rather than the patient. When cancer cells were found in the abdominal cavity of a patient, some doctors tried to discover the primary carcinoma. Sometimes they ended in vain even after the autopsy of the dead patient. In fact, "a cancer patient" should be regarded as "a patient who has contracted cancer" rather than "cancer contracted by a patient." When they provide him or her with treatment and care, doctors and nurses should put emphasis on the patient himself or herself. They should take their patient as a person with physical, psychological, and social needs rather than focusing on his or her organ with physiological or pathological changes. Different people with the same cancer may turn out to have different fates. Some patients with cancer died even though they had their tumor removed, or had their cancerous organs fully cut off, or even had all the surrounding lymph glands removed no matter whether there was a metastasis or not. On the contrary, some patients with cancer survived even though their cancer had not been radically cured or even had not been treated. Here are some other examples. Some patients who were not informed of their advanced cancer still work as usual and even take part in a sports meet as a runner. In contrast, some patients who were informed of their cancer at early stage did not eat and drink for several days in a state of anxiety and were scared to death only in a few days. These examples demonstrate that many doctors only took care of the organs relevant to their specialties and the diseased organs or lesion, so they got the diseased organs cured but damaged other organs crucial for a patient's survival. They couldn't attend to one thing without neglecting the other. Some doctors who did not realize that topical lesion is the signal of a systemic disease or indicates the patient's poor health only focused their treatment on topical lesion. Consequently, the disease did not get cured and the patient died.

1.2 Symptoms Play a Dominant Role in Diagnosing Disease

Symptoms are the main indicators to reflect the expression, severity, progress, and outcome of a disease. However, the same symptom may be shown in different diseases while different symptoms in the same disease. Moreover, the sequence of the symptom manifestation of the same disease in different patients may vary. Some diseases, though very serious, have no corresponding symptoms at all until the advanced stage. Nevertheless, some doctors use a stereotyped approach to the understanding of the disease, comparing its symptoms with what is stated in their textbooks, so they are figuratively called "Dr. Symptom," which means they make a diagnose and treatment of the disease only based on their observation of its symptoms. For example, the doctor gave a patient with severe abdominal pain an injection of highly powerful narcotics, which resulted in the relief of the pain but the patient died in the end. In fact, the pain is just the early symptom of the disease but more severe changes are taking place or will take place in his or her body. The administration of painkillers at will may mask the real cause of the disease and even delay the treatment for the patient. Symptoms, which are various and are always changing, comprise the superficial ones and substantive ones. For an experienced doctor who treated a patient with eight symptoms, he would focus his or her attention on one substantive symptom, and the other symptoms would soon disappear as the result of the proper treatment to the substantive one. In this way, this skillful doctor saved the patient's life. When an inexperienced doctor treated a patient, he or she would administer treatment for each symptom. After the administration of a great amount of drugs, most or even all of the symptoms like cough, fever, and abdominal pain disappeared. As a result, the patient who looked pale and remained in a deep coma died of liver failure due to the overuse of drugs.

1.3 Clinical Examination Plays a Key Role in Diagnosing Disease

Major clinical examinations, such as laboratory testing, medical imaging, and pathological diagnosis, play an important role in the development of clinical medicine and the

practice of conventional treatment. It is true that a hospital cannot be modernized without the rapid development of clinical examination. Likewise, a modern hospital must be equipped with advanced Laboratory Testing Department and Medical Imaging Department. Just as a cleverest housewife can't cook a meal without rice, a clinician with exquisite skills cannot perform his or her tasks in a hospital without them. However, many clinicians pay no attention to the training and practice of the basic diagnostic skills such as "inspection, touching, knocking and acouophonia," or "observation, listening, interrogation and pulse-taking." When a patient with fractured hand and leg went to the hospital, the doctor asked him or her to have his or her bones X-rayed in medical imaging department. After examining the results of CT and MRI, the doctor informed the patient of his or her fractured hand and leg which the patient himself or herself had already known. What's worse, some doctors diagnosed and even treated the disease based on the results of X-ray image, ultrasound scan, blood tests, etc., turning blind to the patient. I once examined the CT image of a patient who was treated in another hospital. I diagnosed the patient as having cirrhosis of the liver by examining his CT image from another hospital. However, the doctor in that hospital diagnosed it as liver cancer and administered percutaneous transhepatic variceal embolization (PTVE) and local chemotherapy to him. Isn't it another disaster fallen upon him when PTVE and local chemotherapy were administered to him who had less normal tissue due to the cirrhosis of the liver? The hospital defended itself in this way: since the patient had already had hepatitis virus infection, PTVE could kill the virus though it had little effect on cancer cells. What a ridiculous explanation! Some young doctors are so dependent on clinical examination in their diagnosis of the disease that they can't carry out their practice without them. They would track down any possible hints of disease through countless examinations so as not to miss them even if the examination results were proven futile and ineffective. If the values of the tests were found on the increase or abnormal image or cells were detected in the patient, he or she was diagnosed as having some disease, and vice versa. Therefore, clinicians have become a slave to clinical examination because they give it first priority in the whole process of practice, including diagnosis of the disease and administration of medicine. In fact, the condition of human body is changing all the time. There are many cases like "the same disease showing different images," "the different diseases showing the same image," "one disease showing many images," and "many diseases showing no image." Once I acted as a supervisor in a reexamination of the postgraduate candidates. I asked them a question "Under what condition will carcinoembryonic antigen (CEA) increase?" They gave three different answers: it would increase if the patient had a cancer, or if she was pregnant, or if he smoked. "Any other possible cause for the increase?" I asked. "None. They are all the answers in our text books." At this moment, one student said that CEA would also increase if something was wrong with examination. It is a quite good answer, totally different from the answer to the question "Under what condition does 1 plus 1 equal 3?" put forward in the intelligence game by a famous Chinese comedian Benshan Zhao. It is this philosophical way of thinking that paved the way for the young man's later success. All the doctors should cultivate this way of thinking. In fact, suffering from cancer, being pregnant, or smoking does not necessarily contribute to the increase of CEA while the decrease of CEA may be related to one of the three cases, showing the complex mechanism of human body. Cancer indicators are not necessarily the determinants of cancer. No absolute thing exists in the world, nor does absolute value exist in medicine. If it does happen, it is due to the small size of the collected samples. During the period of SARS outbreak, a protein detected in SARS victims was found to be 100% positive, but 100% negative in normal people. The finding was taken as a novel approach to detecting SARS virus. Later it turned out that the protein in SARS patient was only related to fever, which can be caused by different diseases with protein positive. Therefore, this protein cannot be regarded as specific to SARS diagnosis. Isn't it so complicated if that protein is only used for diagnosing fever? Clinical thermometer or even our hands and eyes do work.

1.4 Doctors Act as Pharmacists

Drug treatment has been considered as an important means of curing diseases and an indispensable part of medical practice since ancient times. Medical treatment and drugs are so closely related to each other that they are figuratively called "one family." However, there is a great variety of drugs in the market. For instance, cephalosporin, one type of antibiotics, is used in some hospitals with more than 20 types. The same drug not only has different chemical names, brands, and dosage but also shows different efficacy and side effects after administration, which makes the doctors puzzled at their medication. In addition, most doctors would like to give prescription based on the symptoms rather than the disease itself. The first symptom or the most serious one will be treated as priority. One drug will be used to treat one symptom and if it doesn't work another drug or even several drugs will be considered as alternatives with the help of pharmacists. In some cases the symptom worsens; in other cases the symptom disappears but another symptom occurs. What's worse, all his or her symptoms disappear but the patient dies of adverse reaction to drugs. When confronted with such complex cases, the doctors would count on the drug rather than their diagnosis and treatment. Consequently, it is the pharmacist who instructs the doctor to prescribe drug, caus-

ing great confusion in treatment. Once a doctor prescribed erythromycin for a patient with fever, and when the drug was not available in dispensary, the pharmacist dispensed daunorubicin instead. When the nurse asked whether the drug was wrongly dispensed, the pharmacist explained that it was erythromycin of a new generation. In fact, daunorubicin is a kind of anticancer drug. In Chinese, erythromycin is called "Hong Mei Su" and daunorubicin "Rou Hong Mei Su." As a result, a single word variation in the drug name makes the great difference. Here is another story. A patient suffered from liver dysfunction after stents were embedded in his heart. He was taking some drugs when I visited him to hold the consultation. I was surprised to find that he was taking 16 types of tablets, coupled with the damp-removing painkilling ointment. Why did he take so many drugs? The real reason was that because he was a leader of the university, directors of each department showed their great concern for him by prescribing the so-called goodwill drugs, namely, the drugs for prevention. As a result, the drugs heaped up. It is not wrong to prescribe the drugs from their own individual professional angle, but every drug is more or less toxic to some degree and the accumulated toxicity caused great damage to the patient's liver, which almost led him to death. I asked him to stop taking all the drugs except for aspirin for anticoagulation, and finally the patient recovered. The cases indicate that drug administration should be scientific. Traditional Chinese medicine stresses treating diseases in a dialectical way. Chinese medicines are grouped into "Monarch, Minster, Assistant, and Guide." Reasonable matching is the key point. Traditional Chinese medicine stresses the different roles played by different ingredients in a prescription. If the matching is not "One, Three and Five," there must be "One, Five and Seven." One refers to the main ingredient, or called monarch ingredient, to treat the major disease; the minister, assistant, and guide ingredients must be added or subtracted in terms of the symptoms to treat the disease in cooperation with the main ingredient. If a medicine has a conflict with the main ingredients, it may not cure the patient's disease, but worsen his or her disease. Probably, the disease is not cured, but the patient may not lose his or her life.

1.5 Physiological Treatment Is Separated from Psychological Treatment

A patient should be regarded as "a person with a disease or diseases." So not only the "disease" should be cured but also the "person" should be cared about. Although the pathological change in his or her body can be perceived, the psychological suffering is neglected. His or her recovery involves not only the doctor's treatment but also the patient's efforts, without which the disease may relapse or his or her condition may worsen [9]. For example, a young lovelorn lady jumped off a building and was severely injured. The injury might heal through medical treatment but if the psychological problem was not tackled thoroughly, she was likely to commit suicide again by hanging or drowning herself. So both physical and psychological treatment should be applied for her full recovery. With more and more cases like that, it would be impossible to cure all these patients even though we have more doctors.

In the early stage of medical development, owing to low productivity and lack of scientific knowledge, one could not understand the real cause of the disease. At that time psychological consultation played a significant role in the treatment of diseases. The person engaged in this practice was called "witch" or "witch-doctor." There was once a "witch-dominated" era when the role of psychological treatment was so overstressed that people were obsessed with gods and ghosts, resulting in the prevalence of superstitions. The overemphasis on the psychological treatment is totally wrong. To the other extreme, with the development of medical science, psychological treatment was disregarded and even completely denied at a time. Take Chinese Cultural Revolution for example. The campaigns of "Doing away with four olds (old idea, old culture, old custom and old habit), Rooting out the feudal culture, Sweeping away the ghosts and monsters, and Opposing metaphysics" were waged to take the nonmaterial things as pseudoscience, false medicine or idealism, or even ideological problem. Up to now, such ideas, views, and practices are still occurring everywhere and even at the present time. In fact, even if symptoms and even serious ones are shown in some diseases, they cannot be detected through the medical examination, because they are caused by psychological disorders rather than the pathological changes. Curing the mental worries can relieve the symptoms, or even cure the disease. About 30–40% of outpatients with digestive disease recovered in this way. Besides, some psychological disorders caused by organic disease do more harm to the patients than the disease itself. Psychological disorder will be cured as the result of effective treatment of organic disease. In short, psychological disorder or physiological disease sometimes exists independently, but most of the time they coexist and interact as cause and effect. From the perspective of holistic integrative medicine, only when doctors are armed with both medical and psychological knowledge can they treat the intractable diseases.

1.6 Medical Treatment Is Not Well Coordinated with Nursing

The Guideline of National Medical and Health System Reform points out that nursing reform aims at changing the nursing mode, namely, switching "the disease-oriented functional nursing" to "patient-oriented primary nursing" to offer

patients continuous and seamless high-quality nursing services. The old saying "Treatment and nursing account for 30 and 70% in the patients' recovery respectively" highlights the importance of nursing in the disease treatment and patients' recovery. The patients hope to get not only the effective treatment but the holistic nursing as well. Generally speaking, the process of diagnosis and treatment for patients might be short and unconscious while their experience of nursing services is long and conscious. The medical service quality has been greatly enhanced with the involvement of nursing and its staff in the medical service. This transformation and the development of holistic nursing have changed the primary-secondary relationship between doctors and nurses into an equal and cooperative one for patients' recovery [10]. The successful operation lies in the cross-disciplinary cooperation and coordination among surgeons, anesthetists, and nurses. On some occasions, nursing even plays a more important role. Nurses, stereotyped as working under the guidance of doctors, are now supposed to make arrangements for surgeons and anesthetists in the operation room, and supervise them to operate in a standardized way to avoid complications, even medical accidents. In foreign countries, nursing and nursing staff are greatly valued by the doctors and administrative staff and highly respected by patients. However, in China, this new type of cooperative relationship between doctors and nurses has not yet been fully recognized. In fact, nurses should perform the frontline tasks such as drug administration or their observation of patients. However, because of their different traditional roles, doctors and nurses are not well coordinated in such aspects as knowledge mergence in medical teaching and learning, technical coordination, professional complementation, and intercommunication. For example, nursing is not included as a whole in the clinical treatment. Nurses are not asked to participate in case discussion, preoperative discussion, or death case discussion, and even if asked occasionally they only act as foils. As a result, nurses fail to know their essential duty in rescuing seriously ill patients. What's worse, lack of cooperation between doctors and nurses may even cause medical disputes or medical negligence. As mentioned above, "doctors act as pharmacists," and "pharmacists act as drug dispensers." What about the nurses? Nurses act as "nurses who deliver drugs." Most of their working hours are spent on non-nursing work, such as drug dispensation and delivery instead of nursing by the bed. They carry out a variety of medication orders mechanically without any attempt to communicate with the doctors about the patients' condition or treatment. They account for the hospitalization expenses and press for payment rather than offering patients the recovery and psychological consultation. Consequently, doctors and nurses have fewer ward inspections together, and doctors seldom inform nurses of the remedies. So, the cooperation between doctor and nurse is compromised and even clashed. Nurses keep occupied by such physical labor as delivering drugs, giving injections, taking temperatures, and counting pulses, a far cry from the requirements of holistic nursing. Doctors always assign the nursing degree to nurses in their medical orders simply based on the severity of the disease, without considering patients' nursing needs, or other psychological and social factors. For example, when a patient with tertiary care who has almost recovered from a major surgery may suddenly die of pulmonary embolism, it is nurses, rather than doctors, that are usually blamed for their improper inspection. So the nurses have become "the accused." It is obvious that direct cause of this case is the incompatibility of nursing degree with the patient's condition. Since the ancient times, there has been the concept of "integrated medical care." Hippocrates, known as "the father of medicine" by ancient Greeks, used to teach the patients how to gargle and teach the nephropathy patients how to have a rational diet, which developed into "oral care" and "diet nursing" in modern nursing. Shizhen Li, the author of "An Outline Treatise of Medical Herbs," was good at both treating and nursing. He decocted medicinal herbs for the patients and fed them in person, which has become a much-told tale. This is called the "oral administration" in modern nursing. I do not mean that doctors should do nurses' job, or vice versa. Both of them should fulfill their own duty. The point is that doctors should carry out their medical service from the perspective of nursing while nurses from the perspective of treatment.

1.7 Western Medicine Conflicts with Traditional Chinese Medicine

Western medicine and traditional Chinese medicine have developed for a thousand or even thousands of years, even though they belong to different medical schools. As the common wealth of human civilization, both of them have contributed to the survival, reproduction, and development of mankind, though there are some similarities and dissimilarities. However, with their respective features in theories and practices, both of them tend to emphasize their own specialties and advantages. If they are reconciled for the same goal of diagnosing and treating diseases, they could be enriched mutually to form an integrated Western-Chinese medical system, getting the twice results with the half efforts [11, 12]. Unfortunately, their coordination has never made any significant improvement due to constant mutual condemnation and contradiction. In history, Western medicine practitioners looked down upon traditional Chinese medicine practitioners. Here are some examples. Around 1880, the new practitioners of TCM were against the senior ones; with the introduction of Western medicine into China during the Period of Northern Warlords Government, the practitio-

ners of TCM were excluded by the doctors; and until now, they are still negated in society. Some people even openly claim that "traditional Chinese medicine is not scientific." In fact, it is one-sided to put emphasis on the correctness and contribution of either traditional Chinese medicine or Western medicine. For example, Western medicine has advantages in curing acute illnesses while Chinese medicine in curing chronic ones. Western medicine focuses on nidus for the immediate relief with medication or operation, while Chinese medicine treats the body as a whole in order to achieve an overall recuperation, regain vigor, and finally reach the state that "Vital energy exists inside, so pathogenic factors can not prevail." For instance, at present the best medicine for ulcer is proton pump inhibitors with an immediate effect and a rather high cure rate. However, for functional dyspepsia, Lenitive Pill (Baohe Wan) or Agastachis Pill for restoring healthy energy (Huoxiang Zhengqi Wan) may be more effective, since proton pump inhibitors cannot maintain a long-term effect on it. If we give the patients ulcer proton pump inhibitors at the acute phase and Agastachis Pill for restoring healthy energy at the recovery phase, the effect of the treatment will be much better with the integrated methods.

1.8 Treatment Is Prior to Prevention

It is well known but far from well accepted that public health service should mainly focus on the prevention of diseases. It is said that Que Bian, the ancient Chinese medical master, had two elder brothers. Que Bian himself specialized in treating advanced diseases, which earned him great and eternal fame. His second elder brother specialized in treating early diseases, and his eldest brother specialized in treating potential diseases, which is similar to modern preventive medicine. Because of the differences in their specialties, Que Bian's two elder brothers had never gained their fame and still remain unknown. We have no evidence to confirm this story, but one thing is certain that from ancient times to the present, preventive medicine has never aroused enough attention. Even if it did arouse "enough" attention, it is not comparable to that by preclinical medicine, not to mention clinical medicine. In fact, a disease is like bursting flood when it occurs. Which is more important, going downstream for flood fighting and rescuing people or plugging the breach on river banks immediately? The answer is definite. Preventive medicine should have been integrated medicine. The specialization of modern medicine turns the linear thinking pattern of "one disease, one gene; one pathogen, one treatment" into the mainstream in medical development. Public health incidents, such as SARS and H1N1 influenza, have proved that this linear longitudinal treatment is not enough. Instead, we need a comprehensive "point-line surface-body" prevention and treatment, taking "pathogen, disease, population and society" into consideration. Clinical medicine mainly involves the diagnosis and treatment of a disease while the preclinical medicine studies the nature of a disease, but neither of them can prevent such a disease from recurring among different populations in different regions. Based upon the study on factors influencing the health and their effects, preventive medicine aims at illustrating the interrelation between external environment and public health, and subsequently laying down some strategies and measures for prevention [13]. Therefore, preventive medicine itself needs to be integrated with not only the disciplines in preventive medicine, such as epidemiology and labor and environmental health, but also the disciplines in preclinical medicine, clinical medicine, and even social medicine.

It was once believed that with the accomplishment of Human Genome Project, people could discover the secrets of life and disease, and conquer all the diseases [14, 15]. However, the reality is not in line with our expectation. The reason is that genes can only predetermine the genetic predisposition to certain diseases, while most diseases result from the combined effects of environmental factors and organic factors. It is true that preclinical medicine uncovers the pathogenesis of diseases while clinical medicine offers treatment to diseases. But we have to turn to preventive medicine for effective prevention from the "postnatal noxious stimulation" to nip the problem in the bud. When it comes to preventive medicine, people can't help thinking of an emergency with staffs in their protective gear, shouldering a sterilizer and spraying disinfectant everywhere. In fact, this is totally misunderstood. Preventive medicine does much more than that. It can not only offer treatment during and after the incident, but also, more importantly, provide prevention in advance. In short, it can curb not only advanced diseases, but also potential diseases in advance. Suppose a football team of "medicine" in a football match. During the match, clinical medicine acts as the forwards, preclinical medicine acts as coaches to make tactical plans, and preventive medicine serves as the goalkeeper. If the team has a top goalkeeper, the external factors, such as playing home or away, or "black whistles," could do little to the result. So such a team will be unbeatable. Accordingly, preventive medicine should also play a pre- and post-role in integrated medicine. That is, preliminary research must be conducted as the highest priority, and later intervention must be carried on in time and persistently. Therefore, preventive medicine should always run through integrated medicine.

However, the current preventive medicine is clearly separated from clinical medicine and preclinical medicine, and the situation is worsening. Only with the comprehensive integration of preclinical medicine and clinical medicine can preventive medicine offer effective strategies to disease prevention. However, at present the science of medicine is

becoming more and more specialized, which really hinders the development of preventive medicine in every aspect. If this situation continues with treatment over prevention, it is likely that the task, originally accomplished by one doctor in preventive medicine, will require 100 clinical doctors at present. If this tendency goes on, ultimately 1000 or even 10,000 clinical doctors may not be able to solve the problem which one staff in preventive medicine can handle at the early stage.

1.9 Gap Between Urban and Rural Medical Service Is Widening

In China, there exists a huge urban-rural gap in medical service, causing a serious social problem [16]. As a result of the unreasonable distribution of health resources under the current Chinese health system rather than the overspecialization of medicine, this problem is different from the previous eight ones. Only with the integration of medicine can this problem be solved. At present, most of the doctors in rural areas, with the title of general practitioners, are not qualified and doctors in urban areas are mostly specialists without enough competence for general medical service. This situation has resulted from the urban-rural economic gap, the unbalanced hospital distribution, and especially the specialization of urban hospitals over the past several years. On the one hand, rural practitioners desire to work in urban hospitals but they are not competent at special medical work. On the other hand, specialists in urban hospitals are not only unqualified for the general medical work in rural hospitals but also unwilling to work there because of the poor economic and living environment. Consequently, a large number of rural patients are pouring into cities for better medical service, imposing a heavy burden on national transportation. In rural areas quality medical service is not available, directly contributing to inadequate and overly expensive medical services in China. In addition, technical secondary schools and 3-year colleges were banned, which used to train general medical practitioners for rural hospitals. Even though both the central and the local governments are promoting healthcare reform aiming at solving this problem, there is still a long way to go. To sum up, the increasing labor division in society has largely improved the proficiency of people's professional techniques, working efficiency and social prosperity, and living standards. Likewise, the increasing specialization of medicine has greatly promoted the development of medical techniques and the doctors' professional ability. However, with the change of lifestyle and disease spectrum, the specialization has seemingly reached its limit, suggesting that endless "specialization" cannot solve the current medical problems. Unless the problems get settled, the development of modern medicine would not only be hindered, but slip off the track as well. Then, what should we do? We should promote theoretical study on integrated medicine and accelerate the practice of holistic integrative medicine [17].

1.10 Promoting Theoretical Study on Integrated Medicine

To promote researches in integrated medical theories, we must first clarify the following points and set the priorities in theoretical research.

1. With the advance in medical research, the causes of some diseases have been identified. However, in clinic, most of the diseases cannot be attributed to a specific cause. For example, we cannot identify the specific cause of such diseases as primary hypertension and autoimmune because they result from combined effects of several factors. A trauma may even induce the change of more than one system or an organ. Therefore, it is unlikely to know and cure a disease only by one discipline.
2. With the shift of lifestyle, some diseases like cancer and diabetes become incurable to some degree. Specialized treatments may lead to poor life quality and relatively short-term survival, which to some extent may compromise human dignity. Nonetheless, with integrated medical treatments, we can help these patients live with disease and improve their life quality. Integrated medicine not only shows a respect to human dignity, but is a must for humans as well.
3. With the change of natural environment, emerging and re-emerging infectious diseases, like AIDS, SARS, and A (H1N1) influenza, are becoming a threat to humans due to the delay of induced resistance to the diseases. Doctors have such little knowledge about the cause and mechanism of diseases that they could do nothing, much less diagnose and treat the diseases. One single medical discipline is only a drop in the bucket, which cannot win the war against the diseases. To win the war requires the multidisciplinary integration.
4. With the advent of the ageing stage, the average life span of Chinese people has increased by more than 30 years during the past 50 years. During these additional 30 years, the physical condition of Chinese people will change as a result of the interplay with the nature and physical senescence. These physiological or pathological changes still remain uncertain or under-investigated. It needs multidisciplinary integration to resolve the present and future medical problems caused by ageing.
5. With the development of medical technology, many diagnostic techniques and therapies, which were beyond imagination in the past, have already been applied to treat many thorny cases. However, the development of medi-

cine seems to have hit its bottleneck. The classical medical techniques have been proved effective in solving only local problems rather than global or systemic ones. The sustainable development of medicine must count on the integration of medical knowledge and technology.

6. With the march of modern society, the incidence of disease is increasingly related to social reality which triggers a variety of psychological problems. If doctors only focus on physical diseases and ignore psychological problems, it is by no means to treat or cure a large number of patients even though we have more hospitals and doctors.

Integrated medicine is a reformation of the traditional medicine, symbolizing a new stage of development from specialization to integration in the medical course. It is not a regression but a progress. It aims at achieving the following goals: the integration of biological factors and that of psychological, social, and environmental factors, and the integration of the most advanced medical discoveries in all life-related areas and that of the most effective clinical experience in all medical specialties. It also requires us to analyze a problem with not only linear, one-dimensional way of thinking in natural science, but also nonlinear multidimensional way of thinking in philosophy. Through this thinking mode and the reintegration of the above four integrations, a more comprehensive, more systemic, and more scientific new medical knowledge system would be established, which accords with natural laws, health maintenance, and disease prevention, diagnosis, and treatment. This is the unity of "rearrangement" and "combination." In this sense, integrated medicine should be defined as holistic integrative medicine (HIM). Although HIM has not yet been fully recognized, it will become a worldwide trend and international frontier of medical investigation, which will be definitely tough and complicated. As we all know, it has already taken thousands of years for both traditional Chinese medicine and Western medicine to evolve from generalization to specialization, with the former lagging behind the latter on the way. Therefore, integration is doomed to be difficult because it defies traditional theories, established practices, academic authority, and force of habit. In addition, medicine has developed into an enormous theoretical system and will keep growing. In this system, we have to differentiate the primary from the secondary, the cause from the effect, the predecessor from the successor, and the truth from the false. We should try to attain the essence out of the dross and strip the false off the true by analyzing the nature of the problem and its relevant factors. In the era of knowledge explosion, what to be integrated and how to integrate are worthy of extensive and intensive study. The more we want to integrate, the more complex the integration is. Therefore, we should take scientific methods and forward-looking strategies to achieve the integration in the historical context. The outcomes of integration must be able to stand the test of practice. We need to highlight the advantages of promoting HIM and point out the disadvantages of impeding it, and establish excellent models of promoting HIM so that we can wipe out the stereotypes completely and scientifically and form new concepts. In the promotion of HIM, we should theoretically illuminate that everything, regardless of whether it is as large as the universe or as small as human body, should be regarded as a system within which all internal elements are closely related. This idea requires doctors to have a global picture instead of only a local one.

Although there are some similarities between HIM and general practice, their differences are marked. General practice requires general practitioners to be expert in one field and versatile in others. But their competence developed from the established basic theories and common practice is only the sum of ordinary abilities, like the sum of A + B + C. HIM emphasizes rational and scientific integration of the most advanced theories and the most effective experience, which is like the multiplication of A × B × C. The former is a quantitative increase which can be achieved by ordinary people while the latter indicates a qualitative leap which can be achieved by only a few talents. For instance, Specialist A knows how to rub red lotion with high concentration. Specialist B knows how to rub blue lotion with high concentration. General Practitioner C can rub both the red and blue lotions but with lower concentration. But Doctor D was so well trained with HIM that he or she can invent green lotion by integrating red with blue lotion with the effect of both lotions, which can be interpreted as "Green comes from red and blue but is better than both."

Although there are some similarities between HIM and translational medicine (TM), their differences are evident. TM translates preclinical findings into clinical application to test their values and then optimizes the preclinical research [18]. It finally takes the advantage of preclinical findings to improve human health through the process.

HIM is different from complementary and alternative medicine (CAM). CAM views Western medicine as mainstream medicine and underestimates other schools of medicine as nonmainstream medicine. CAM is a school discriminating against the viewpoints of other schools [19].

Although there are some similarities between HIM and evidence-based medicine (EBM), their differences are obvious. EBM lays stress on making rational clinical decisions which may result in desirable efficacy and fewer side effects on the basis of the available evidence from the investigation of a group of patients [20], while HIM represents the cognition of human health and diseases with emphasis on comparison, analysis, and integration of theories and practice. HIM aims at exploring the most optimal therapeutic methods with the best curative effects and establishing a new medical knowledge system.

The transformation of the medical model is an extremely complicated project. We need to define HIM with high accuracy by carefully clarifying its connotation and denotation. In order to define HIM accurately, we should revise, modify, and improve connotation and denotation through discussion. On the one hand, medical workers should be encouraged to realize the urgency and importance of promoting HIM. It is known that the changes of more than one type of genes and cells or one organ take place in the development of a certain disease. The strong regulatory and protective mechanism may cause overall changes of the functions and structures of the systems in human body. In addition, the development and outcome of the changes are related to environment, dietary habit, and even interpersonal relationship. So it is necessary to diagnose and treat diseases with comprehensive consideration of HIM. On the other hand, it is noteworthy that we should not deny the importance of medical specialization [21]. Specialists are and will be playing their part for their therapeutic efficacy and accuracy at present and in quite a long period afterwards.

1.11 Accelerating the Advancement of HIM Practice

Truth can only be verified through practice. HIM is both a profound and practical science, which needs to be unceasingly enriched, improved, and verified in practice. It is a never-ending process from theory to practice, back to theory, and again to practice. We should adopt the following strategies to accelerate this process [1, 17].

1.11.1 Organizing Academic Conferences on HIM

The conferences aim at popularizing the concept of HIM, exchanging academic achievements on HIM, and drawing on the experience of HIM practice. At the initial stage, we could hold seminars based on certain topics or certain diseases, such as holistic prevention and control areas for hepatitis B, or holistic prevention strategies for tumor. We could invite the scholars in translational medicine, clinical medicine, and preventive medicine to the seminars and foster discussions on the theory, the diagnostic and therapeutic methods, and the preventive strategies from different perspectives, so that we could reach an agreement and make some guidelines, which will be amended or improved step by step. Based on the experience gained from the seminars, we could hold national HIM conferences. In this way, we could solve the problem that scholars from different disciplines never contact with each other, which is similar to the case that people who are nourished by the same river never greet each other.

1.11.2 Establishing HIM Academic Associations

We should attract the talents in HIM and invite the specialists in preclinical medicine, clinical medicine, and preventive medicine to join the HIM academic associations to promote the development of HIM. We could set up the Holistic Integrative Medicine Association of Chinese Medical Association, officially named the Chinese Association of Holistic Integrative Medicine, which could have several branches such as Integrated Gastroenterology Society and Integrated Cardiology Society. In this way we could treat a disease with different methods from different specialties to avoid the phenomenon that "scholars tend to scorn each other."

1.11.3 Publishing the Journals on HIM

We should start the publication of Journal of Chinese Holistic Integrative Medicine and its affiliated journals such as Integrated Gastroenterology Journal, Integrated Cardiology Journal, and so on to report the latest achievements on HIM in every discipline. In this way we could gradually deal with the problem that when a dispute over an academic issue arises, only a person of authority has the final say.

1.11.4 Publishing a Series of Books, Textbooks, or Monographs on HIM

The publication of these books could solve the problem that many books are various in cover but similar in content due to the fact that the authors copy one another.

1.11.5 Setting Up HIM Institutes

We should carry out in-depth specialized research in HIM using techniques for network information analysis as the main approach in addition to the methods applied in the evidence-based medicine. As mentioned above, HIM aims at integrating the most advanced theoretical achievements in every field with the most effective clinical experience in each discipline in a systematic way and achieving the effect of "multiplication" rather than the effect of "addition." However, over the past 200 years, both world population and medical knowledge have been growing exponentially. For example, in the 1980s, the number of biomedical journals worldwide reached 40,000 and is predicted to double every 20 years. Here is another example. Knowledge is outdated at a faster pace than before. In the eighteenth century a person's knowledge became outdated and obsolete in 100 years but now it is in 5 years that a person's knowledge should be

updated. In the coming 20 years, the amount of knowledge in biomedicine alone will be equivalent to a total amount of knowledge in all fields over the past 2000 years. It is self-evident that human brain can neither "memorize" all the information nor "keep up with" the growth of knowledge. Although the computer cannot rival the human brain in terms of intelligence, it can easily beat the human brain in memory capacity and logic operations. With information integration, we could optimize the integration of the most advanced medical knowledge from various disciplines, and the most effective clinical experience in every specialty, thereby boosting the reintegration of the integrated medical knowledge and experience so as to construct a new system of medical knowledge, which will lead to a new leap in the development of medicine, which is also called data-based medicine or information-based medicine. It covers the following aspects:

- Establishing a platform for preclinical and clinical research in HIM
- Keeping the residents' health records
- Providing information about disease prevention, establishing a system for diagnosis and treatment, and providing analysis of treatment and recovery
- Providing comprehensive knowledge about drug interactions and clinical guidelines
- Integrating specific information of patients
- Establishing strategies of making clinical decisions and communication mechanism for experts in related fields
- Providing methodology for evaluating and predicting the curative effect
- Offering integrated patient health information (electronic health records or electronic medical records of patients from birth to present)
- Developing software assisting independent diagnosis and treatment (such as prevention, diagnosis, risk assessment of health, treatment program, clinical testing and examination, clinical medication and operation, enhancement of patient's confidence)
- Constructing the informationalized environment, including the residents' health records, disease control (through local area network, the Internet of things, and the Internet), family health records, family health information system, home care information system, prehospital emergency care information system, emergency information system, long-term care information system, referral information system, hospital information system (including outpatient station, ward station, admission management system, LIS system, PACS system, the doctor's advice system, ICU monitoring system, and operation management system)
- Keeping electronic medical records, etc.

In this way we could help medical workers discard the dross and select the essential, and get rid of the false and retain the true at the era of knowledge explosion.

1.11.6 Setting Up HIM Wards

The integration should be launched among several disciplines as a trial. The disease-oriented integration of internal medicine, surgery, and other related disciplines has already been carried out in some American hospitals over the past few years. Recently, the hospital-within-hospital mode taken in some general hospital in China is a good attempt for HIM. The general wards and intervention wards in some hospitals are to some extent in line with HIM. For example, vascular intervention wards and minimally invasive wards are HIM wards where internal medicinal and surgical techniques are integrated. Strictly speaking, the current general wards are the ones that deal with a variety of diseases whereas ICUs are the wards that deal with acute severe diseases through various techniques. HIM should develop in accordance with ICU mode. The clinic of Preventive Medicine and Health Care Maintenance (CPMHCM), or "Preventive Clinic," should be set up. By integrating this clinic with outpatient clinics, clinical practices such as preventive care and checkup service are organically combined, changing the isolated practice of the vaccination or checkup service. By combining the distinctive advantages of preventive and clinical medicines, such an integrated clinic can provide more comprehensive services for the public, including health education, checkup service, and health records. In this way, we could help patients overcome the difficulty in finding the right department to get their diseases diagnosed and treated due to non-patient-oriented diagnosis and treatment.

1.11.7 Offering HIM Courses

The transformation of medical education mode should be accelerated by gradually changing the system-based or discipline-based mode, which requires freshmen to learn with an overall view. The currently advocated training of general practitioners is beneficial to the development of HIM. In the teaching practice of HIM, the integrated courses should be set up for medical students before their internship, accelerating their shift towards doctors equipped with HIM. What's more, the system of cultivating such doctors should also be established. For instance, resident doctors are required to have a prolonged rotation, and newly recruited doctors to receive training in different departments for 3 or 4 years. In this way, they will gradually develop into doctors with the ability of analyzing and solving medical problems. Furthermore, senior practitioners should regularly attend lectures on the development of HIM so as to be equipped with HIM knowledge so that they are able to diagnose and treat patients with HIM knowledge and skills. HIM teaching is by no means the denial of current teaching methods, but the integration and systematization of current teaching methods and contents. In this way, the problem that medical

students are short of HIM knowledge will be gradually solved, and some misconceptions will also be corrected such as "The top priority for medical students is to become ophthalmologists, next is to become surgeons, and the worst is to become physicians" and "Compared with general practitioners, specialists feel more secure and face less trouble."

1.11.8 Providing Continuing Education on HIM

The HIM continuing education can be provided either by the public health organizations at all levels or by some medical colleges and universities headed by academic institutions such as the Chinese Medical Association. First, HIM training should be provided for the medical workers in grade-three class-A hospitals across the country, and then extended gradually to those in grassroots hospitals. Second, HIM knowledge should be added to the Qualification Examination for Licensed Physicians so as to motivate doctors to autonomously learn and apply HIM knowledge. Third, in medical colleges and universities, HIM courses should be offered as compulsory courses in the postgraduate education programs or in on-the-job training for teachers, avoiding the current problem of overspecialization of medicine. In this way, we could solve the problem that a doctor who has been assigned to work in a medical department for lifetime will become a specialized doctor with limited knowledge and skills.

In summary, it takes more than 1000 years for medical science to develop from generalization to specialization. Although specialization has its advantages, it must fit the contexts. Overspecialization fails to help healthcare providers develop a comprehensive view on the truth of life, and the secrets of human body. Without the overall view, a doctor diagnosing a disease is like a blind man figuring out the image of an elephant just by feeling some part of it. Without the overall view, a medical researcher doing medical research is like a man seeing the trees but not the forest. Medical development requires integration, and the fruit of this integration is HIM. HIM, in essence, is to ensure that medical diagnosis and treatment are not organ centered but patient centered and not symptom oriented but disease oriented. HIM requires doctors to act as doctors in the real sense of the term instead of pharmacists, who diagnose and treat patients based on clinical experience rather than laboratory results. HIM is to make sure that medical workers could put the same weight on treatment and nursing, Western medicine and traditional Chinese medicine, and treatment and prevention. However, it should be noted that HIM discipline does not necessarily perform all the medical tasks in a general hospital, nor require HIM practitioners to be competent for all the medical service. The doctors in HIM discipline must bear it in mind that they must treat their patients with the guidance of HIM and make them have higher survival rate, longer life span, and better life quality than those treated by other doctors and even themselves in the past. That is the basic requirement for both HIM and healthcare professionals in HIM.

References

1. Fan D-M. Holistic integrative medicine. Am J Digest Dis. 2014;1(1):22–36.
2. Fan D. General remarks on holistic integrative medicine (in Chinese). Negative. 2012;3:3–12.
3. Sierpina V, Kreitzer MJ, Anderson R, Hanaway P, Shannon S, Sudak N. The American Board of Integrative and Holistic Medicine: past, present, and future. Explore. 2010;6:192–5.
4. Mantri S. Holistic medicine and the Western medical tradition. Virtual Mentor. 2008;10:177–80.
5. Zuskin E, Lipozencić J, Pucarin-Cvetković J, Mustajbegović J, Schachter N, Mucić-Pucić B, Neralić-Meniga I. Ancient medicine—a review. Acta Dermatovenerol Croat. 2008;16:149–57.
6. Li S, Xu H. Integrative Western and Chinese medicine on coronary heart disease: where is the orientation? Evid Based Complement Alternat Med. 2013;2013:459264.
7. Lam TP, Sun KS. Dilemma of integration with Western medicine – views of traditional Chinese medicine practitioners in a predominant Western medical setting. Complement Ther Med. 2013;21:300–5.
8. Chan E, Tan M, Xin J, Sudarsanam S, Johnson DE. Interactions between traditional Chinese medicines and Western therapeutics. Curr Opin Drug Discov Devel. 2010;13:50–65.
9. Ventegodt S, Andersen NJ, Merrick J. Holistic medicine: scientific challenges. ScientificWorldJournal. 2003;3:1108–16.
10. Mariano C. Holistic nursing as a specialty: holistic nursing—scope and standards of practice. Nurs Clin North Am. 2007;42:165–88.
11. Song JJ, Yan ME, Wu XK, Hou LH. Progress of integrative Chinese and Western medicine in treating polycystic ovarian syndrome caused infertility. Chin J Integr Med. 2006;12:312–6.
12. Liu X, Zhang M, He L, Li Y. Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS). Cochrane Database Syst Rev. 2012;10:CD004882.
13. Broadbent A. Philosophy and preventive medicine. Prev Med. 2012;55:575–6.
14. Baetu TM. Genes after the human genome project. Stud Hist Phil Biol Biomed Sci. 2012;43:191–201.
15. Hood L, Rowen L. The human genome project: big science transforms biology and medicine. Genome Med. 2013;5:79.
16. Yip W, Hsiao WC. The Chinese health system at a crossroads. Health Aff. 2008;27:460–8.
17. Fan X, Yang Z, Fan D. Further discussion on holistic integrative medicine (in Chinese). Med Philos. 2013;34:6–11. 27
18. Littman BH, Di Mario L, Plebani M, Marincola FM. What's next in translational medicine? Clin Sci. 2007;112:217–27.
19. Pan SY, Gao SH, Zhou SF, Tang MK, Yu ZL, Ko KM. New perspectives on complementary and alternative medicine: an overview and alternative therapy. Altern Ther Health Med. 2012;18:20–36.
20. Duggal R, Menkes DB. Evidence-based medicine in practice. Int J Clin Pract. 2011;65:639–44.
21. Weisz G. The emergence of medical specialization in the nineteenth century. Bull Hist Med. 2003;77:536–75.

Part II

Intracrainal and Intraocular Pressure Related Diseases

Understanding Primary Open-Angle Glaucoma from the Perspective Beyond Ophthalmology

2

Ningli Wang, Xiangxiang Liu, and Diya Yang

2.1 Introduction

Primary open-angle glaucoma has been recognized for several hundred years. Initially, it was defined as an eye disease of characteristic structural change of optic nerves and specific visual change caused by increased intraocular pressure (IOP). However, when we comprehended the development and progress of glaucoma only limiting to perspective of the eye itself, we could hardly interpret some problems we encountered clinically. For example, in clinical practice, we would notice some glaucoma patients with IOP in normal range, some ordinary people with IOP higher than normal range without any glaucomatous optic neuropathy (GON), some glaucoma patients with continuing worsen of optic nerves and visual fields in spite of their IOP under-control by drugs or surgeries and also, some glaucoma patients usually combining with nervous system diseases at the same time. Are those phenomena occasional or there are some correlations yet not discovered? In order to answer the above questions, the ophthalmologist must expand their vision, and not only consider the eye as a part of the whole body, but also think with "integration" concept, and comprehend comprehensively beyond eyeball itself. In this section, the author will regard the eye as part of the central nervous system, and propose an innovative theory of "trans-lamina cribrosa pressure gradient" and a concept as "glaucoma being a disease of central visual pathway" through combining circulation of both topical ocular and body fluid. This chapter intends to take people's understanding of the primary open-angle glaucoma as an example so that readers will feel the charm of "integration" and proceed from this concept in future research and work. Perhaps this change of perspective can open up a new world.

2.2 Glaucoma, Disease with a Long History

Glaucoma is one of the most ancient diseases that have accompanied human being all along. The recognition of glaucoma starts from the era of Hippocrates in the fourth century B.C. At that time, the seawater-like "greenish grey" appearing in the eyes of the aged accompanied with no vision was described as "glaykoseis." In the "Shen Nong's Herbal Classic" in the Qin and Han Dynasties, there were records of "green blind eye disease" and "green wind eye disease". However, people at that time identified the disease merely by judging the color change and vision decrease; therefore, other diseases including cataract and other eye diseases were also included in the diagnosis, which (was) (hard to) distinguishing from glaucoma.

It's the first time humans have linked eye pressure to the disease of glaucoma that until 1622, British doctor Banister (1570–1626) discovered and recorded a patient with no improvement in visual acuity after cataract removal and his eyeball was in a tough state. After that, in the entire eighteenth and nineteenth centuries, the abnormal phenomenon of "hardened eyeball" was recorded by physicians consistently. It is not until in 1832 Sir William Lawrence first comprehensively described the symptoms of these phenomenon, and defined this condition as "glaucoma," and described "acute glaucoma." In 1864, Littell from American Wills Ophthalmic Hospital more accurately described the disease as "a condition of vision loss with a greenish-grey eyeball similar to amaurosis," and added "hardness of eyeball" to the description of the disease. McKenzie, a Scottish ophthalmologist (1791–1868), considered in the first classic ophthalmic textbook *Practical Treatise of the Diseases of the Eye* that glaucoma is caused by excessive fluid accumulation in retina, and proposed to treat glaucoma by performing fluid

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_2

drainage by puncturing at eyeball wall to release IOP. This is the first try to treat glaucoma through reducing IOP, marking the beginning of glaucoma treatment, and the treatment has been passed on until today.

2.3 The Confusion About Glaucoma in "Modern Times"

In 1851, the invention of ophthalmofundoscope by Hermann von Helmholtz, a German ophthalmologist (1821–1894), became a revolution in the history of ophthalmology development. In 1857, Albrecht von Graefe, another German ophthalmologist (1828–1870), firstly observed and described "excavated optic disc" anomalies of angle-closure glaucoma; this was the first time to diagnose glaucoma by judging the defect of optical disc structure of fundus other than ocular surface color and hardness, which was a great leap for the recognition of glaucoma.

In 1905, the invention of Schiøtz ophthalmotonometer ushered in an era of quantitative measurement and evaluation of glaucoma. After that, IOP became a key index used in the diagnosis and treatment of glaucoma. In 1940s, with the invention of gonioscopy examination, we gradually realized that not all glaucoma belongs to the same kind of disease, but mainly includes primary angle-closure glaucoma (PACG) and primary open-angle glaucoma (POAG).

PACG is the optic neuropathy mainly caused by increased IOP resulted from mechanical angle closure, and the pathogenesis is clear, while the cause of POAG (74% of total glaucoma) is still unclear. Classic theory among previous Western regards that the main cause of POAG is the optic nerve impairment occurring in the lamina cribrosa caused by increased IOP. Therefore, the study of POAG mainly focuses on the cause of disorder of intraocular aqueous humor drainage and the cause of optic nerve impairment occurring in optic disc and lamina cribrosa currently. Subsequently, there emerged various theories, such as that increased IOP is caused by MYOC gene, Schlemm's canal collapse, trabecular meshwork functional disorder, mechanical injury, or optic disc ischemia.

2.4 Clinical Concerns Existing in Glaucoma

Backed up by above theories and hypotheses, the cognition of POAG is becoming more and more thorough that glaucoma is a series of optic nerve degenerate diseases with increased IOP (absolute/relative) as the main risk factor, specifically manifested by pressure-related optic neuropathy and progressive vision defect [1]. Under the guidance of glaucoma treatment system using IOP as the indicator for a long time, various drugs and surgeries have been developed and used in order to lower the IOP. However, more and more evidences proved that increased IOP is not the essential cause of glaucoma, and previous theories and hypotheses can only partially explain it, and even less for the question that why optic neuropathy exists in POAG.

According to clinical observation, most POAG patients have normal tension glaucoma (NTG). We performed 24-h monitoring on POAG patients in Handan Eye Study, and found that about 83% of POAG patients in China had NTG, with peak IOP lower than 21 mmHg [2, 3]. Thus, as the IOP of such patients is in normal range, then why do they still have glaucomatous optic neuropathy?

Interestingly, a confusing fact is that there are also some patients having IOP constantly higher than normal range, while they have not had optic nerve impairment all along, who are called as patients with ocular hypertension (OHT). After a 5-year follow-up study, the international ocular hypertension treatment study group (OHTS) found that only 9.5% of patients with OHT eventually developed to have glaucoma [4]. Then, why would not the patients with IOP higher than normal range have optic neuropathy?

Even more confusingly, in the IOP reduction treatment performed on POAG patients, the progress of optic neuropathy still cannot be prevented in some patients after the IOP has been reduced to target IOP. Meanwhile, in patients with normal IOP, IOP reduction treatment was effective to some patients by slowing down or preventing the progress of optic neuropathy. In still a proportion of patients, the optic nerve impairment will not progress even without any IOP reduction treatment, and the patients will stay in a static period of glaucomatous optic neuropathy. Then why is the IOP reduction treatment unable to stop the progress of glaucomatous optic neuropathy in some patients even though their IOP had been reduced, and why is the optic nerve impairment stays in static period even without IOP reduction treatment in some other patients?

For a long time, the above clinical questions cannot be answered and they also overthrew our traditional concept on the relationship between glaucoma and IOP!

From the historical process of human understanding of glaucoma, every point of our understanding of glaucoma builds on previous erroneous observation. And only a new improvement in methodology and epistemology might lead to further knowledge on the essence of glaucoma. Then, do we need to "recognize" the glaucoma from the very beginning again?

2.5 Glaucoma and Central Nervous System: Re-understanding Glaucoma with "Integration" Concept

The glaucoma is a series of diseases characterized with chronic, progressive nervous degenerate changes of retinal ganglion cells (RGCs). Anatomically, the ganglion cell bod-

ies are in the retina; the axons become medullated fibers after going through lamina cribrosa and gathered as the optic nerve, which go through intraorbital segment, intracanalicular segment, and intracranial segment, form the optic chiasma, where nasal optic nerve fibers from both sides cross to the other side; the temporal never fibers and the nasal nerve fibers from the other side gathered as the optic tracts reach the lateral geniculate body where synapse of nerve fibers and axons terminate in the visual cortex. Therefore, the RGCs are parts of the neuron in the central nervous system, which means that they are an extension of the brain. Various intracranial changes, such as inflammation, hemorrhage, and tumor, can all spread to optic nerves, causing optic nerve compressive or inflammatory change, and leading to occurrence of corresponding symptoms of vision defect or vision acuity decrease.

In addition, compared with other 11 pairs of cranial nerves, the optic nerve is the only cranial nerve surrounded by cerebrospinal fluid (CSF) and dural sheath along the entire line. It goes through a narrow optic canal, and enters the orbit from intracranial space until reaching posterior eyeball. Therefore, abnormal changes of biochemical components in CSF or CSF pressure changes can all lead to the impairment of optic nerves and eyeball itself, causing occurrence of changes, such as optic disc edema.

Therefore, the eyes and brain are organismically inseparable, and their intrinsic internal connection has vital significance to the physiology and pathology of eyes and optic nerves.

2.5.1 Glaucoma and Impairment of Upper Neuron

Previous studies believed that the occurrence of pressure-induced RGC axonal injury of glaucoma will lead to RCG apoptosis by means of Wallerian degeneration and degeneration of the entire RGC axon. However, Schlamp et al. [5] proved in the DBA/2 J mouse model for experimental glaucoma that chronic IOP increase led to slight pressure-induced injury of RGC axon, and then atrophy and degeneration occurred from axonal end to RGC body by means of axon degeneration (dieback). Crish et al. [6] also found in the DBA/2 J mouse model for experimental glaucoma that axonal end injury occurred before retinal RGC injury. This is to an extent the interpretation why RGC loss cannot be detected in some glaucoma individuals with vision defect [7, 8]; therefore, even if RGC body exists in retina, axon degeneration would still lead to loss of connection from RGCs to central visual pathway, and thus failure of visual signal transmission. This suggests that retinal ganglion cell impairment of glaucoma does not start from the eye, but from axonal end, and progresses to the eye.

The glaucoma does not only lead to RGC axonal impairment, but it might also lead to injury of transsynaptic degeneration, just like what happens in other degeneration diseases of central nervous system, such as Alzheimer's disease. That is, the already injured neuron passes on the injury through synaptic junction to originally intact neurons. Crawford et al. [9] found in primate glaucoma model that change of cytochrome oxidase activity occurs in all layers of lateral geniculate body corresponding to increased IOP. Weber [10] and Yucel et al. [11] found obvious atrophy in large cell and small cell layers, neurons, and interneurons as well. Yucel et al. [12, 13] also found that neuron loss in lateral geniculate body is linearly correlated to mean IOP, and the increase of mean IOP level in small cell layer can lead to the rise of atrophy degree of survived neurons. Meanwhile, it was also observed in koniocellular pathway that CaMK-II immunoreaction targeting the K-cell marker was weakened, suggesting that neurochemical change of blue-yellow pathway for color sense might occur in early intraocular hypertension stage. Gupta et al. [14] also noted in a macaque model of glaucoma that the chronic IOP increase induced reduction of quantity and distribution of dendrites in magno- and parvocellular layers of lateral geniculate body.

Zhang et al. [15] noted in a rat model of acute intraocular hypertension that on day 3 after acute high IOP, atrophy and neuron loss simultaneously occurred in retina, lateral geniculate body, and superior colliculus; besides, on day 1 after acute IOP increased, colocalization of GFAP and GS staining of Muller cells could be detected, which suggested that the neurogliocytes were activated earlier than RCG loss, and transsynaptic degeneration of glaucoma may not necessarily need continuous high IOP, and the activation of neurogliocyte may participate in neuron degeneration after increasing IOP.

Therefore, from above studies, it can be concluded that for POAG, increased IOP may not directly damage RGCs, but at first induce the injury of upper neurons of lateral geniculate body, superior colliculus, etc., and then cause atrophy and degeneration of RGC body by axon degeneration.

However, the injury of upper neurons caused by glaucoma may not limit to lateral geniculate body and superior colliculus, but the neurons in visual cortex are also injured pathologically. Gupta et al. [16] found in the autopsy of glaucoma patient that pathological injury occurs in intracranial optic nerves, lateral geniculate body, and visual cortex, of which the injured part and degree were correlated to the part and degree of visual field loss and optic disc injury, manifested by superior visual field loss in both eyes of the patient, and there is atrophy of corresponding inferior optic nerves, decrease of phosphorylation level of nerve fibers, atrophy of posterior-lateral neurons of lateral geniculate body, thinning of visual cortex, etc. Besides, with the examination of a patient with POAG with MRI, atrophy of lateral geniculate body was found [17]. At the same time, functional magnetic

resonance imaging (fMRI) found low blood oxygen level-dependent (BOLD) signal in the visual cortex of patient with POAG [18].

Qing et al. [19] found primary visual cortex corresponding to the central normal vision of patient with POAG, and BOLD signal of primary visual cortex of glaucoma decreased, while BOLD signal intensity and visual field are negatively correlated. This suggested that the residue central vision of glaucoma patient might have been injured in primary visual cortex level; therefore protecting the residual central vision may have more significance for the patient.

Apart from visual cortex injury, other central parts involving optic nerve fibers might also have glaucomatous injury. As described above, about 10% of nerve fibers in optic tract will not project on lateral geniculate body, in which some nerve fibers projecting on suprachiasmatic nucleus are from a type of melanopsin-containing RGC (mcRGC) related to diurnal rhythm. Chiquet et al. [20] found in a rat model of glaucoma that injuries occurred not only on the entire visual pathway but also on the suprachiasmatic nucleus; Wang et al. [21, 22] found in a rat model study of acute high IOP that, after acute IOP elevation, the quantity of mcRGCs in retina significantly decreased, and suprachiasmatic nucleus injury was found at the same time. The correlation of mcRGCs with diurnal rhythm regulation in human suggests that the glaucoma may cause injury of non-form sense pathway simultaneously, and the patient with glaucoma may need to be further cared on life quality related with sleep.

It can be seen from the above studies that the optic nerve injury of glaucoma is not merely limited to the eye but also affects the entire visual pathway, even the non-form sense pathway. This also partially explains the reason for the phenomenon that even after the IOP of some glaucoma patients is reduced to normal, their visual function still continues to be even worse, which is possibly due to continuous impairment of upper neurons; meanwhile the treatment approaches and measures applied currently are only limited to the eye, the protection of the entire visual pathway is neglected.

2.5.2 Glaucoma and Cerebrospinal Fluid Circulation

All along the time, under the influence of the classic theory of mechanical injury of POAG, it is believed that glaucomatous optic neuropathy is caused by increasing IOP which leads to the structural changes in lamina cribrosa and disorder of axoplasmic flow in ganglion cell axons. However, if we review this situation from a holistic perspective, would we see an entirely different story?

Generally, the axons of retinal ganglion cells converge at optic nerve head, and become optic nerves after going through lamina cribrosa; thus the lamina cribrosa structure separates the optic nerves into two sections with different pressure. Viewing from the anatomical structure of lamina cribrosa, the tissues before lamina cribrosa are subject to the effect of IOP, and the IOP exerts backward force to the lamina cribrosa; meantime, posterior lamina cribrosa is subjected to the pressure of CSF coming through subarachnoid space, which generates forward force to the lamina cribrosa. The difference between the IOP before lamina cribrosa and the subarachnoid space CSF pressure of optic nerves behind lamina cribrosa is the "translamina cribrosa pressure difference" (TLPD). Analyzing merely from the perspective of biomechanics, both the increase of IOP and the decrease of subarachnoid space CSF pressure can raise TLPD and thus it may cause backward force to lamina cribrosa, leading to optic nerve impairment.

Ren et al. [23] from Beijing Tongren Hospital collected 43 POAG patients (14 with a normal IOP, and 29 with an elevated IOP) who had received cerebral spinal fluid pressure (CSF-P) measuring by lumbar puncture to exclude nervous system disease and 71 patients without glaucoma but with other nervous system diseases as control group. The study found that the CSF pressure was lower in the high IOP glaucoma group (11.7 mmHg) than in the control group (12.9 mmHg) ($p < 0.001$), and the CSFP was significantly lower in the normal IOP glaucoma group (9.5 mmHg) compared to that in the high IOP glaucoma group ($p < 0.05$). They also found that TLPD showed relatively high correlation with visual field loss of patients with glaucoma ($p < 0.001$). In another study, Ren et al. [24] found that CSFP was significantly higher in patients with ocular hypertension (OHT) (16.0 mmHg) than that in the control group (12.9 mmHg) ($p < 0.001$).

This is the first prospective study in the world that found the lowering CSFP in NTG patients, which may lead to higher TLPD which causes optic neuropathy. However, patients with OHT have a higher CSFP that TLPD may remain the same, and thus no such optic neuropathy occurs. Based on these studies' achievement, Beijing Intraocular and Intracranial Pressure (iCOP) Study Group was established.

Meanwhile, the research team from Duke University also proved the above conclusion through a retrospective study. They compared the CSF pressure by lumbar puncture between 29 POAG patients and 49 normal patients of control group, and found that the CSF pressure was ($p < 0.00005$) significantly lower in patients with POAG (9.2 mmHg) than in the control group (13.0 mmHg) [25]. Berdahl et al. [26] in another retrospective study compared CSFP of 11 patients with NTG, 57 patients with high-tension POAG (HTG), 27 patients with OHT, and 105 non-glaucoma patients of control group. They found that the CSF pressure was ($p < 0.0001$ and $p < 0.01$) significantly lower in both NTG and HTG patients (8.7 and 9.1 mmHg) than in the control group (11.8 mmHg), while the CSF pressure was significantly higher in the OHT patients (12.6 mmHg) than in the control group ($p < 0.05$).

In addition, considering high risk of measuring orbital subarachnoid space CSF pressure directly, above studies all used cerebral spinal fluid pressure (CSF-P) by lumbar puncture as study parameter. Nevertheless, CSF pressure measured by lumbar puncture directly reflects the pressure in the spinal subarachnoid space, not the orbital subarachnoid space CSF pressure around the optic nerves. Then has the orbital subarachnoid CSF pressure in NTG patients decreased?

According to the Poisson theory of physics, seeing optic nerve sheath as an elastic tissue, when the CSF pressure in orbital subarachnoid space increases, it will cause increasing force to the optic nerve sheath, which makes it to have elastic expansion. Therefore, Beijing iCOP Study Group proposed a new hypothesis that the CSFP in orbital subarachnoid space is lower in NTG patients, so the width of orbital subarachnoid space in NTG patients should be narrower than HTG patients and normal controls.

Based on this hypothesis, Wang et al. [27] from iCOP study group collected 21 NTG patients, 18 HTG patients, and 21 normal control volunteers and performed 3.0 T MR. It was found that the orbital subarachnoid space width was indeed lower in the NTG patients than in normal control group and HTG patients, with statistically significant difference in the comparison. The results suggested that the CSF pressure in orbital subarachnoid space decreased, which further proved our preliminary hypothesis.

Based on this study, iCOP Study Group further studied the relationship among CSF pressure, basic parameters, and orbital subarachnoid space width, and obtained noninvasive intracranial pressure evaluating formula through calculation with multiple regression [28]. And this noninvasive intracranial pressure measuring method was verified in study populations of three epidemiological studies, which included Beijing Eye Study, Handan Eye Study, and Central India Eye Study [29, 30]. From the study of large population, it was found that POAG is correlated to the trans-lamina cribrosa pressure difference between IOP and ICP, but not IOP.

Beijing iCOP Study Group believed that the TLPD between intraocular and intracranial pressure might be the main cause leading to optic neuropathy in POAG. For NTG and OHT patients, simply classifying and judging by IOP as the only manifestation can hardly interpret the cause of disease, whereas TLPD may be the key basis for interpreting the above clinical problems.

Nonetheless, above studies only revealed the phenomenon that the NTG patients have relatively low CSF pressure, but did not necessarily mean that the decreased CSF could lead to glaucomatous optic neuropathy. Therefore, using lower CSFP animal model to observe occurrence of glaucomatous optic neuropathy could elucidate the relationship between increased TLPD and glaucomatous optic but this does not necessarily mean that the decreased CSF could lead to glaucomatous optic.

Yang et al. [31] from iCOP Study Group performed surgeries on monkeys with the method of lumbar-peritoneal cerebrospinal fluid (CSF) shunting, and built the animal model for intracranial hypotension. The study reduced intracranial CSF pressure of monkeys by CSF shunting, to increase the TLPD between IOP and orbital subarachnoid CSF pressure. This study proved that increasing TLPD by simple chronic intracranial pressure reduction could cause glaucomatous optic neuropathy; as after 6–14 months of continuous status as with lower intracranial pressure and increased TLPD in monkeys, it showed significant reduction in retinal nerve fiber layer (RNFL) thickness, and there were diffuse nerve fiber layer defects and optic cup enlargement. Among them, two monkeys had progressive reduction in retinal nerve fiber layer thickness, and the RNFL thickness loss rate was around 13.7% and 27.3%, respectively; they also showed significant reduction in the area and volume of the neuroretinal rim. One monkey had a splinter-like optic disc hemorrhage at inferior temporal side of right eye, and during the subsequent follow-up, although there was no obvious change in RNFL thickness, the quadrant area RNFL thickness analysis revealed that the RNFL thickness in the optic disc hemorrhage area significantly decreased. According to the animal experiment, this study verified the relationship between increased TLPD and glaucomatous optic neuropathy, and revealed that the IOP is not the only factor causing glaucomatous optic neuropathy, but the increase of TLPD between IOP and ICP is the main factor causing optic neuropathy of glaucoma.

By comprehensively considering the results of this animal experiment study and previous clinical studies, iCOP Study Group firstly proposed that the increase of TLPD is the main cause leading to glaucomatous optic neuropathy. According to the results of current studies, the classification of the so-called glaucoma with normal IOP or OHT is irrational, while the POAG is only a nervous degeneration disease of characteristic optic neuropathy caused by the increase of TLPD between IOP and ICP. Mechanical and hemorheological factors can be involved in the pathological injury process after increasing TLPD. This is the first time to combine the pluralism of the pathogenesis of POAG into monism, and it is the re-recognition of POAG with the concept of holistic integrative medicine (HIM), and it will change the clinical practice of POAG.

2.6 Glaucoma and the Body: Re-understanding Glaucoma with "HIM" Concept

The degenerate diseases of central nervous system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, have similar basic

pathological change to that of optic nerve change of glaucoma, which all manifested by axoplasmic transport disorder, transsynaptic degeneration, and chronic progressive degeneration of axons and neurons, and eventually ended to neuronal apoptosis. Among them, Alzheimer's disease is most similar to glaucoma.

Yoneda et al. [32] found that β-amyloid level (1–42) in the vitreous body was significantly lower and Tau protein level increased in patients with glaucoma and diabetic retinopathy, compared with the normal controls, which are consistent with the change of these two characteristic kinds of proteins in the CSF in patients with an Alzheimer's disease [32, 33]. Gupta et al. [34] also found abnormal change of Tau protein in the retina of patients with glaucoma. McKinnon et al. [35] detected in rat chronic OHT model that caspase-3 activated in RGCs, while caspase-3 is able to split amyloid precursor protein (APP) to produce neurotoxic segment, such as β-amyloid, suggesting that the death of RGCs in glaucoma may be similar with Alzheimer's disease at the molecular level, both having β-amyloid neurotoxic effect involved. Guo et al. [36] proved that the comprehensive treatment with multiple targets of β-amyloid formation and gathering process could reduce glaucoma RGC apoptosis in vivo, suggesting that the intervention strategy targeting at characteristic protein synthetic pathway of Alzheimer's disease is also suitable for the treatment of glaucoma.

Apart from the study evidence of the possible occurrence of characteristic protein and molecular level change of Alzheimer's disease in the glaucoma, moreover, some study data evidence also revealed that the patients with Alzheimer's disease also had manifestation of optic atrophy and RGC loss [37, 38]. In addition, more study data showed that a patient with Alzheimer's disease had an increased morbidity of POAG [39]. Bayer et al. [40, 41] found based on an investigation among four nursing homes in Germany that the morbidity of glaucoma for the patients with the Alzheimer's disease was 25.9%, significantly higher than that of the control group (5.2%). In another retrospective study, it was found that the morbidity of glaucoma for the patients with Alzheimer's disease was 24.5%, and that for the patients with Parkinson's disease was 23.7%, suggesting that the morbidity of glaucoma significantly increased in both diseases. In Asia, Tamura et al. [39] found that the morbidity of glaucoma for Japanese patients with Alzheimer's disease was 23.8%, significantly higher than that of control group (9.9%), and all glaucoma patients with Alzheimer's disease were with NTG, and their IOP values did not differ from the non-glaucoma patients with Alzheimer's disease. Lu et al. [42] found in patients with Alzheimer's disease of early stage that the thickness of retinal nerve fiber layer was significantly lower than that of control group, suggesting that patients with Alzheimer's disease had degeneration of retinal nerve fiber even at the early stage.

More and more evidence showed the correlation between the glaucoma and Alzheimer's disease; however, it is still unclear whether one disease leads to the occurrence of another or both diseases are caused by the same risk factor. Tamura et al. researched and found that the levels of alleles of apolipoprotein *E(APOE) ε4* in the glaucoma patients with Alzheimer's disease were not different from those of non-glaucoma patients with Alzheimer's disease, suggesting that *APOEε4* may be not the common risk factor of the two diseases. Recently, some other studies even suggested that *Helicobacter pylori* infection might be the common risk factor for both of them [43]. Besides, Kessing et al. [44] found in a national disease investigation that the number of the Alzheimer's disease in POAG patients was not different from that of the control group, suggesting that POAG is not the risk factor leading to the increase of Alzheimer's disease morbidity.

However, according to the in-depth study of correlation between glaucoma and CSF pressure based on iCOP studies [23–31], it is believed that the intracranial pressure of patients with Alzheimer's disease is in relatively low state after encephalography, suggesting that low intracranial pressure may be closely correlated to the occurrence of optic nerve injury of glaucoma in patients with Alzheimer's disease.

2.7 Summary

According to the above introduction, glaucoma is a disease correlated to the whole body. The optic neuropathy caused by increased IOP only accounts for about 17% of all POAG patients, and the cause of disease for the other 83% of POAG patients is not IOP. Merely focusing on IOP, there will inevitably be classifications such as "normal tension glaucoma" and "OHT syndrome," due to the limitation of methodology and epistemology.

Under the concept of HIM, we gradually recognized that over 80% of POAG is caused by reasons other than the eye itself, and so far it is believed that intracranial pressure is one of the primary factors. With further study, more factors might be considered. Such as venous pressure, as the intracranial pressure itself is also subject to the influence of venous pressure. A series of the simplest body parameters, such as body height, weight, blood pressure, and nutrition status, may contain more hints of unknown effect, and play an important role in regulating TLPD. Therefore, POAG is correlated to cardiovascular system, digestive system, blood system, nervous system, etc., and it is a systemic disease manifested in the eye.

POAG is superficially manifested in the eye, but has the essential cause in the whole body. The HIM concept changes focusing from a small topical holistic outlook of the organism, and places microscopic evidence in the textual research

of macroscopic thinking, and thus it would be an integration based on comprehension of details and a great leap in methodology and epistemology.

References

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–11.
2. Liang YB, Friedman DS, Zhou Q, et al. Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. Invest Ophthalmol Vis Sci. 2011;52(11):8250–7.
3. Wang NL, Friedman DS, Zhou Q, et al. A population-based assessment of 24-hour intraocular pressure among subjects with primary open-angle glaucoma: the Handan Eye Study. Invest Ophthalmol Vis Sci. 2011;52(11):7817–21.
4. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):701–13. discussion 829–830
5. Schlamp CL, Li Y, Dietz JA, et al., Progressive ganglion cell loss and optic nerve degeneration in DBA/2J mice is variable and asymmetric. BMC Neurosci, 2006. 7:66.
6. Crish SD, Sappington RM, Inman DM, et al. Distal axonopathy with structural persistence in glaucomatous neurodegeneration. Proc Natl Acad Sci U S A. 2010;107(11):5196–201.
7. Swanson WH, Felius J, Pan F. Perimetric defects and ganglion cell damage: interpreting linear relations using a two-stage neural model. Invest Ophthalmol Vis Sci. 2004;45(2):466–72.
8. Su JH, Deng D, Cotman CW. Transneuronal degeneration in the spread of Alzheimer's disease pathology: immunohistochemical evidence for the transmission of tau hyperphosphorylation. Neurobiol Dis. 1997;4(5):365–75.
9. Crawford ML, Harwerth RS, Smith EL 3rd, et al. Glaucoma in primates: cytochrome oxidase reactivity in parvo- and magnocellular pathways. Invest Ophthalmol Vis Sci. 2000;41(7):1791–802.
10. Weber AJ, Chen H, Hubbard WC, et al. Experimental glaucoma and cell size, density, and number in the primate lateral geniculate nucleus. Invest Ophthalmol Vis Sci. 2000;41(6):1370–9.
11. Yücel YH, Zhang Q, Weinreb RN, et al. Atrophy of relay neurons in magno- and parvocellular layers in the lateral geniculate nucleus in experimental glaucoma. Invest Ophthalmol Vis Sci. 2001;42(13):3216–22.
12. Yücel YH, Zhang Q, Gupta N, et al. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. Arch Ophthalmol. 2000;118(3):378–84.
13. Yücel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. Prog Retin Eye Res. 2003;22(4):465–81.
14. Gupta N, Ly T, Zhang Q, et al. Chronic ocular hypertension induces dendrite pathology in the lateral geniculate nucleus of the brain. Exp Eye Res. 2007;84(1):176–84.
15. Zhang S, Wang H, Lu Q, et al. Detection of early neuron degeneration and accompanying glial responses in the visual pathway in a rat model of acute intraocular hypertension. Brain Res. 2009;1303:131–43.
16. Gupta N, Ang LC, Noël de Tilly L, et al. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. Br J Ophthalmol. 2006;90(6):674–8.
17. Gupta N, Greenberg G, de Tilly LN, et al. Atrophy of the lateral geniculate nucleus in human glaucoma detected by magnetic resonance imaging. Br J Ophthalmol. 2009;93(1):56–60.
18. Duncan RO, Sample PA, Weinreb RN, et al. Retinotopic organization of primary visual cortex in glaucoma: comparing fMRI measurements of cortical function with visual field loss. Prog Retin Eye Res. 2007;26(1):38–56.
19. Qing G, Zhang S, Wang B, et al. Functional MRI signal changes in primary visual cortex corresponding to the central normal visual field of patients with primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2010;51(9):4627–34.
20. Chiquet C, Drouyer E, Woldemussie E, et al. Consequences of glaucoma on circadian and central visual systems. J Fr Ophtalmol. 2006;29(7):847–51.
21. Wang HZ, Lu QJ, Wang NL, et al. Loss of melanopsin-containing retinal ganglion cells in a rat glaucoma model. Chin Med J. 2008;121(11):1015–9.
22. Huaizhou W, Jie H, Ningli W. The effects of acuter intraocular pressure elevation on melanopsin-containing retinal ganglion cells. Chin Ophthalmic Res. 2009;27:558–62.
23. Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology. 2010;117(2):259–66.
24. Ren R, Zhang X, Wang N, et al. Cerebrospinal fluid pressure in ocular hypertension. Acta Ophthalmol. 2011;89(2):e142–8.
25. Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. Ophthalmology. 2008;115(5):763–8.
26. Berdahl JP, Fautsch MP, Stinnett SS, et al. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. Invest Ophthalmol Vis Sci. 2008;49(12):5412–8.
27. Wang N, Xie X, Yang D, et al. Orbital cerebrospinal fluid space in Glaucoma: The Beijing iCOP Study. Ophthalmology. 2012;119(10):2065–73.
28. Xie X, Zhang X, Fu J, et al. Noninvasive intracranial pressure estimation by orbital subarachnoid space measurement: the Beijing Intracranial and Intraocular Pressure (iCOP) study. Crit Care. 2013;17(4):R162.
29. Jonas JB, Wang N, Wang YX, You QS, Xie X, Yang D, Xu L. Body height, estimated cerebrospinal fluid pressure and open-angle glaucoma. The Beijing eye study 2011. PLoS One. 2014;9(1):e86678.
30. Jonas JB, Nangia V, Wang N, et al. Trans-lamina cribrosa pressure difference and open-angle glaucoma. The central India eye and medical study. PLoS One. 2013;8:e82284.
31. Yang D, Fu J, Hou R, et al. Optic neuropathy induced by experimentally reduced cerebrospinal fluid pressure in monkeys. Invest Ophthalmol Vis Sci. 2014;55:3067–73.
32. Yoneda S, Hara H, Hirata A, et al. Vitreous fluid levels of beta-amyloid((1–42)) and tau in patients with retinal diseases. Jpn J Ophthalmol. 2005;49(2):106–8.
33. Engelborghs S, De Vreese K, Van de Casteele T, et al. Diagnostic performance of a CSF-biomarker panel in autopsy-confirmed dementia. Neurobiol Aging. 2008;29(8):1143–59.
34. Gupta N, Fong J, Ang LC, et al. Retinal tau pathology in human glaucomas. Can J Ophthalmol. 2008;43(1):53–60.
35. McKinnon SJ, Lehman DM, Kerrigan-Baumrind LA, et al. Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. Invest Ophthalmol Vis Sci. 2002;43(4):1077–87.
36. Guo L, Salt TE, Luong V, et al. Targeting amyloid-beta in glaucoma treatment. Proc Natl Acad Sci U S A. 2007;104(33):13444–9.
37. Hinton DR, Sadun AA, Blanks JC, et al. Optic-nerve degeneration in Alzheimer's disease. N Engl J Med. 1986;315(8):485–7.
38. Blanks JC, Hinton DR, Sadun AA, et al. Retinal ganglion cell degeneration in Alzheimer's disease. Brain Res. 1989;501:364–72.
39. Tamura H, Kawakami H, Kanamoto T, et al. High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. J Neurol Sci. 2006;246(1–2):79–83.
40. Bayer AU, Keller ON, Ferrari F, et al. Association of glaucoma with neurodegenerative diseases with apoptotic cell death:

Alzheimer's disease and Parkinson's disease. Am J Ophthalmol. 2002;133(1):135–7.
41. Bayer AU, Ferrari F, Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. Eur Neurol. 2002; 47:165–8.
42. Lu Y, Li Z, Zhang X, et al. Retinal nerve fiber layer structure abnormalities in early Alzheimer's disease: evidence in optical coherence tomography. Neurosci Lett. 2010;480:69–72.
43. Kountouras J, Zavos C, Gavalas E, et al. Normal-tension glaucoma and Alzheimer's disease: helicobacter pylori as a possible common underlying risk factor. Med Hypotheses. 2007;68(1):228–9.
44. Kessing LV, Lopez AG, Andersen PK, et al. No increased risk of developing Alzheimer disease in patients with glaucoma. J Glaucoma. 2007;16(1):47–51.

Intracranial and Intraocular Pressure-Related Diseases

3

Diya Yang, Ningli Wang, and Yunxiao Sun

3.1 Introduction

The retinal ganglion cells in the closed eyeball converge into the optic nerve, which passes out the eye through the lamina cribrosa, and is surrounded by the three layers of meningeal tissues which communicate with cerebrospinal fluid system of brain, and then projects on the lateral geniculate body—this is the visual way of anatomical knowledge what we are familiar with, which is well learned by all surgeons of ophthalmology, neurology, and head and neck; however, for a long time, experts in different area kept on just focusing on diseases of their own specialized subjects, digging in some research directions more sophisticated but narrow, while ignoring the necessity of integration underlying the basis of anatomy. Analyzing with the thinking pattern of integrative ophthalmology (IO) and mainly directed by the pressure correlation between the two closed chambers, this text puts forward the new concept of "intracranial and intraocular pressure-related diseases" based on the anatomical basis; introduces the primary epidemiology characteristics of the intracranial and intraocular pressure-related diseases; discusses the clinical characteristics and current research of the damage to the optical nerve due to the intraocular pressure (ICP) and the intracranial pressure (IOP) difference increase, including situations as IOP > ICP and ICP > IOP; and lists the possible mechanism of disorders of communication between intracranial and intraocular cavities such as Terson syndrome and eyes with silicone oil tamponade, high myopia, and so on. Starting from this text, hopefully readers might reflect on eye diseases from the perspective of IO, break down the boundaries of different disciplines and departments, and make the diseases having eye syndromes get more comprehensive understanding.

3.1.1 Intracranial and Intraocular Pressure-Related Diseases: Anatomy-Based Integrative Concept

The human optic nerve tissue is located in the ocular cavity and intracranial cavity, two separate, closed-pressure chambers. Due to the hardness of the skull wall and the non-expansion of the skull, the changes of the pressure in the intracranial cavity might cause different levels of damage to the nervous tissues. At the same time, the eyeball is also a closed sphere, with an expansion degree extremely small, and thus the change of intraocular pressure can cause different levels of damage to various tissues inside the eyeball.

The axons of retinal ganglion cells in the eye converge into the optic nerve at the site of optic disc, pass through the wall of the eyeball and into the subarachnoid cavity in the orbit, and continue going into the skull. As there is always a certain pressure gradient (about 5–11 mmHg) between ICP and IOP, when either of them changed, the optic nerve would have injuries because of the shear force generated by the change of the pressure gradient between the two cavity pressure where the optic nerve is. Therefore, any change in ICP or IOP may result in pressure-related lesions of optic nerves.

At the same time, not only the intraocular cavity and intracranial cavity are two relatively closed spaces, but also communication between each other is still possible under certain circumstances, which leads to material exchange between intraocular cavity and cranial cavity, generating various kinds of rare clinical signs and symptoms. Nonetheless, whatever the type of communication between the two chambers would be, the pressure difference is always

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_3

an essential condition for the material exchange and flow here as well.

Therefore, on the basis of special anatomical configuration of intraocular cavity and cranial cavity, the pressure gradient changes between ICP and IOP will inevitably bring a series of related symptoms, leading to intracranial and intraocular pressure correlation optic nerve damage or cranial eye communication disorders; here, we collectively refer to as "intracranial and intraocular pressure correlation diseases."

3.1.2 Epidemiology of Intracranial and Intraocular Pressure-Related Diseases

Most neurosurgical diseases can cause increased ICP, e.g., intracranial space-occupying lesions, intracranial infections, craniocerebral injuries, cerebral anoxia, poisoning, and endocrine dysfunction; among them, craniocerebral tumor is one of the ten most common of fatal tumors, with a prevalence of 130.8 per 100,000 persons, and it is estimated that there are about two million brain tumor patients in China. At the same time, along with the widespread use of high-speed vehicles and the highly advanced construction industry, the incidence of craniocerebral injury has become one of the most important causes of death and disability in young people (incidence: 250/100,000 per year), among which there are 40% accompanied by uncontrollable increase of ICP, causing patients lifelong disability and even death, as estimated.

In addition to the secondary reasons, there are many patients with idiopathic intracranial hypertension (IIH), which is approximately 1.56/100,000, and the prevalence is up to 85.7/100,000 people in obese women; with the rapid development of social and economic level, the obesity population in China is increasing, and the prevalence of IIH is expected to increase in the future.

Moreover, the same as the diseases having increased ICP, many neurological diseases may also be accompanied by decreased ICP, such as Alzheimer's disease and spontaneous intracranial hypotension (SIH) syndrome. Taking Alzheimer's disease as an example, the prevalence rate of the elderly in China is 3–7%, and the number of patients with Alzheimer's disease in China is more than six million, which is expected to exceed 20 million by 2050. Changes of ICP will certainly cause optic nerve damage of different degrees to the patients, leading to decreased vision and even blindness; many patients even go to the hospital first for the reason of vision declines, and then would be diagnosed as with the increase or decrease of ICP.

Not only the changes of ICP but also the changes of the IOP can result in the occurrence of optic nerve damage, the most direct among which is glaucoma. Epidemiological data showed that the prevalence of primary angle closure glaucoma in China was 0.5%, and the prevalence of primary open angle glaucoma (POAG) in China was 1.0%. With the aging of the population, the number of glaucoma patients in the world is expected to increase to 79.64 million by 2020, and 11.2 million may develop to be with binocular blindness because of glaucoma.

In addition to the primary glaucoma, many secondary factors will also result in increased IOP, such as trauma, use of corticosteroids, and glaucoma with pigment dispersion; this part of patients with secondary glaucoma accounts for 18% of the total number of patients with POAG in the Asian population. Moreover, with development of intraocular surgery and increase of surgical volume, hypotony syndrome occurs in more and more patients, which could also lead to changes of optic pressure gradient environment for optic nerve and result in injuries.

According to incomplete statistics, the incidence of blindness caused by the change of pressure gradient is 10% of all the optic nerve injuries. Thus, with current Chinese population calculated as 1.4 billion, about 30 million people in China are threatened by intracranial and intraocular pressure-related impairment of optic nerve, while 3 million of them are blind due to the impairment, accounting for 50% of China's blind population. What is more frightening is that the optic nerve damage caused by changes in the pressure gradient is irreversible, and once it happens vision would never be restored. Therefore, the most important issues today shall include strengthening the prevention and early intervention of optic nerve injury caused by pressure gradient, reducing the incidence of blindness caused by optic nerve injury due to pressure gradient change, improving the quality of life of patients, and reducing the economic burden of society.

3.1.3 Optic Nerve Damage Related to Intracranial and Intraocular Pressure

3.1.3.1 Optic Nerve Damage Caused by the Increased Intraocular-Intracranial Pressure Gradient (IOP > ICP)

In general, there is a certain pressure gradient between IOP and ICP (around 5–11 mmHg); IOP increases or ICP decreases would cause increase of the pressure gradient between the two pressure chambers where the optic nerve is located, resulting in shear force that causes optic nerve damage.

Beijing Tongren Hospital iCOP Group performed the prospective study for making clinical observation of patients with high-tension glaucoma (HTG), normal-tension glaucoma (NTG), and ocular hypertension (OHT), and found that the increase of pressure gradient between IOP and ICP is the main cause of glaucoma optic nerve damage. The low ICP in the patients with the so-called NTG caused optic nerve dam-

age because of the increase of the difference between IOP and ICP. Meantime, in patients with OHT, the relatively high ICP makes the pressure difference between IOP and ICP not to increase, thus avoiding the possible optic nerve damage caused by OHT.

At the same time, this group established a noninvasive ICP measuring method, through the confirmatory study on the large-scale natural population in three epidemiological surveys, Beijing Eye Study, Handan Eye Study, and Central India Eye Study, and found that the thickness of the retinal nerve fiber layer is negatively correlated with the intraocular-intracranial pressure gradient, while POAG is mainly related to this pressure gradient.

Subsequently, in order to further prove the causal relationship between the intraocular-intracranial pressure gradient and optic nerve damage in glaucoma, the research team carried out a study with rhesus monkey model for intracranial hypotension by surgeries of lumbar-peritoneal cerebrospinal fluid (CSF) shunting. The study confirmed that the decrease of the ICP can cause glaucoma optic nerve damage by increasing the pressure gradient: after 6–14 months of continuous intracranial hypotension and increased intraocular-intracranial pressure gradient, the monkeys' retinal nerve fiber layer thickness decreased significantly, and diffuse nerve fiber layer defects and enlargement of the optic cup occurred.

So far, the theory of optic nerve damage caused by the pressure gradient between the IOP and the ICP was established by the iCOP study group, which solves the problem of glaucoma that cannot be answered by the theory of IOP and mechanical stress. Multifactor theory for the reason of optic nerve damage of POAG was merged into a unitary factor as trans-lamina cribrosa pressure. This theory has been evaluated as a "milestone" on the way of discovery and contribution in the clinical practice of glaucoma by international ophthalmological community.

3.1.3.2 Optic Nerve Damage Caused by the Increased Intraocular-Intracranial Pressure Gradient (ICP > IOP)

However, the increase of intraocular-intracranial pressure gradient is not the only way to have a stress-related optic nerve injury. ICP may also exceed IOP and lead to the optic nerve damage because of the intracranial-intraocular pressure gradient increases.

Intracranial hypertension is the main cause of the increased intracranial-intraocular pressure gradient, which can lead to optic nerve damage. Many neurological, neurosurgical, and non-neurological disorders may ultimately be mainly manifested by intracranial hypertension. Many patients with intracranial hypertension, especially in patients with idiopathic intracranial hypertension (IIH), often lack systemic expression, with symptoms firstly showed in eye, such as the presence of amaurosis fugax, diplopia, progressive vision loss, and even blindness. The optic disc edema can be seen in the fundus examination of the eye, and the retinal vein would be found tortuous, dilating, and bleeding.

Hypotony syndrome is another major cause of optic nerve damage in intracranial and intraocular pressure gradient increase. With the widespread operation of intraocular surgery, hypotony postoperation is becoming more and more common in ophthalmologic surgery. Due to the IOP lower than ICP, the retinal vein flows back slowly, which can lead to macular edema, optic disc edema, nerve fiber layer thickening, retinal vein tortuous dilatation, etc., a series of clinical symptoms, and even may damage the patients' visual function when it is serious.

In recent years, with the rapid development of the space industry, human beings have lived longer and longer under zero-gravity conditions in space. The national space agency (NASA) found in the latest study that the long-time visual experience in low gravity will lead to complication such as hyperopic refractive drift, macular edema, optical disc edema, and choroidal folds. It is believed that these clinical signs may be related to long-term space life and increase of ICP, and the visual and optic nerve damage was caused by the increase of intracranial-intraocular pressure gradient.

It can be seen from the above content that the optical nerve damage clinical signs, respectively, caused by increased intraocular-intracranial pressure gradient and intracranial-intraocular pressure gradient are opposite, which is specially shown in the posterior pitting or uplift of optic disc, thinning or thickening of nerve fiber layer, and so on. Canceling the increase of pressure gradient is a common means in the treatment of these two kinds of diseases, and adjusting only one of the IOP or ICP may not achieve good clinical effect, while the pressure gradient' overall regulation may be the direction of future clinical treatment.

3.1.4 Disorders of Communication Between Intracranial and Intraocular Cavities

Apart from the optic nerve damage caused by the intracranial and intraocular pressure-related diseases, in certain circumstances, intraocular cavity and intracranial cavity may have a communication between each other, which can lead to relatively rare clinical signs and symptoms, such as Terson syndrome and eyes with silicone oil tamponade, high myopia, optic disc pit, morning glory syndrome, optic disc drusen, congenital optic disc defect.

Terson syndrome is mainly intravitreous hemorrhage secondary to intracranial retinal hemorrhage, which can lead to severe visual impairment. The most direct reason for intra-

vitreous hemorrhage is probably that the intracranial subarachnoid blood reaches the eyeball along with the perineural subarachnoid space, and then diffuses into intravitreous cavity through the lamina cribrosa; another possibility lies in that increased ICP causes blockage of retinal vein backflow and then retinal vein hemorrhages in the vitreous.

For some patients silicone oil was filled inside vitreous after vitrectomy, and silicone oil droplets may pass through the lamina cribrosa holes into the subarachnoid space because of the intraocular hypertension. This is the intracranial-intraocular communication situation.

Peripapillary atrophy with large area may happen in some of the high myopia patients, and there may be a staphyloma in the optic disc or beside the optic disc, which may make the eye material break through the vitreous cavity and get into the perineural subarachnoid space, leading to complete communication between perineural subarachnoid and intraocular space, and then the vitreous body mixed with the cerebrospinal fluid.

The intracranial-intraocular communication disorders are clinically not common, as the reasons for them are always related to the anatomical structure as the neighborhood relationship between intraocular cavity and intracranial cavity, and the pressure gradient between them. Therefore, the intracranial and intraocular communication disease can be thought as the intracranial and intraocular pressure-related diseases.

3.2 Conclusion

All the time, whether the optic nerve damage is caused by IOP or ICP, the equipartition belongs to the ophthalmic or neurosurgery. Due to the division of function department, as neurology, neurosurgery, and ophthalmology belong to different departments, each expert focuses on the disease diagnosis and treatment of his/her own discipline, and often ignores the overlap of disciplines; thus it is difficult to think from the prospective of other disciplines for diagnosis and treatment of patients, for which the role of pressure gradient between IOP and ICP for optic nerve damage is often neglected. Especially for patients with IOP and ICP problems at the same time, simply working on from the perspective of one department cannot fundamentally solve the problem or save the patient's vision, which is also one of the important reasons of difficulties of diagnosing and treating for intracranial and intraocular pressure-related diseases.

Therefore, for these diseases, the symptoms are in the eye, but belong to the category of systemic diseases; collecting diseases of the same kind together from the perspective of HIM, and establishing disciplines focusing on intracranial-intraocular pressure-related diseases for diagnosis, treatment, and further study on them, would lead to in-depth understanding of this kind of disease.

Idiopathic Intracranial Hypertension and Optic Nerve Damage

4

Jidi Fu and Yunxiao Sun

4.1 Introduction

Idiopathic intracranial hypertension (IIH) is a kind of familiar disease for neurological physicians, a syndrome which takes headaches, optical disk edema, and some other signs and symptoms related to increased intracranial pressure as the main clinical manifestations, while imaging examination shows no intracranial space-occupying lesions, vascular lesions, hydrocephalus, or other related intracranial lesions, with normal cerebrospinal fluid composition. In the past, patients with IIH could only be related to ophthalmology for evaluation of optic nerve morphology and status of visual field. However, by integrating lamina cribrosa district into the whole optic nerve pathways by ophthalmologists, people gradually realize that the cerebrospinal fluid circulation around the optic nerve is also related to the eye disease, such as glaucoma. It may provide a good control model for the study of glaucoma. We hope that this chapter, on the one hand, can make eye doctor know more about IIH, including the historical evolution, epidemiology, pathogenesis, clinical manifestation, standard diagnosis, and treatment of this disease; on the other hand, we hope to inspire the reader to recognize the eye diseases from the perspective of craniocerebral diseases.

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4.1.1 Introduction

Idiopathic intracranial hypertension (IIH) is also named as pseudotumor cerebri (PTC) or benign intracranial hypertension (BIH). It refers to the symptoms and signs of intracranial hypertension (ICH), such as headache and optic disk edema, while the imaging examination did not identify intracranial space-occupying lesions, vascular lesions, hydrocephalus, or other related intracranial lesions, which belong to a group of clinical syndromes with normal components of cerebrospinal fluid (CSF). It often occurs in obese women with reproductive age, yet atypical cases can also occur in men, children, and older adults. Although it has been more than 100 years since the first detailed description, the pathogenesis of IIH is still unknown. Over a hundred years, researchers have proposed a variety of hypotheses, most around the cerebrospinal fluid circulation dynamics and the endocrine and metabolism of adipose tissue, but they still failed to well explain the reason for the favor of disease occurrence in the obese women of childbearing age and why obvious cerebral ventricular enlargement is not shown. IIH has main symptoms as headache, transient blurred vision, pulsatile tinnitus, visual impairment, diplopia caused by abducens paralysis, etc.; possible nonspecific meningeal irritation signs as nausea, vomiting, light flashing, etc.; and less common symptoms as cervical radiculopathy, retrobulbar pain, facial pain, etc. And it is mainly manifested in clinical examination as visual impairment, e.g., optical disk edema and visual field defect, which usually remains stable, while gradual or sudden increase is also possible, even causing blindness in severe cases. At present, various methods for treating this disease are all lack of large-scale, randomized, controlled study, as the main purpose of treatment is to reduce intracranial pressure, to relieve typical symptoms of ICH such as headaches, and to prevent visual impairment. The primary treatment measures include lifestyle changes for reducing weight and using medication, and surgical treatments for severe or acute visual impairment patients to reduce intracranial

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_4

pressure and improve vision, which include lumboperitoneal shunting (LPS), ventriculoperitoneal shunting (VPS), optic nerve sheath fenestration (ONSF), intracranial venous sinus stenting, and so on.

4.1.2 History

There have been multiple names in the history of IIH, and its diagnostic criteria have been changed many times. In 1893, Quincke [1] described the disease in detail for the first time. In his article, Quincke described the clinical manifestation for a set of IIH cases with signs and symptoms such as headache and optical disk edema, and with normal CSF composition also attributed the cause of the increase of abnormal CSF secretion. As there was no abnormality found in CSF component, Quincke referred to this disease as "serous meningitis." Soon after that in 1904, Nonne [2] first proposed the term "PTC," describing a group of patients with ICH, but not intracranial tumors. Because ICH is mainly seen in patients with intracranial tumors, and these kind of cases were in an awkward position in diagnosis at that time, the term "PTC" was introduced. Given the high incidence of otitis media at the time, he believed that many cases from this group of patients may have intracranial venous sinus thrombosis secondary to the otitis media, which was the idea emphasized again by Symonds [3] in 1931, having the disease get another name called "otitic hydrocephalus." During this period, because the concept of knowledge was not unified, various names such as "toxic hydrocephalus," "hypertensive meningeal hydrops," " ICP without brain tumor," "brain swelling of unknown cause," and "papilledema of indeterminate etiology" all appeared in the literature, while "PTC" was still widely used in this period. With the development of ventriculography, people learned more and more about this disease. Ventriculography showed that the ventricular volume of patients with IIH was normal or decreased, thus distinguishing it from hydrocephalus, and taking a step towards its real pathogenesis. In 1937, Dandy [4] reported 22 patients with "PTC," and put forward the diagnosis standard of the disease for the first time. The criteria include the following five aspects: (1) there are signs and symptoms of ICH, e.g., headache and optical disk edema; (2) the CSF pressure is greater than 25 cm H_2O; (3) there is no focal neurological sign except the abducens nerve palsy; (4) composition of CSF is normal; and (5) no intracranial occupying lesion is found with cerebral ventriculography, and the ventricular volume was normal or decreased. In 1955, Foley [5] suggested to use "BIH" to emphasize that the disease was not caused by the "tumor" which often showed malignance in clinical process. After that, "BIH" became the most popular name for the disease. However, in 1969, Buhcheit [6, 7] put forward that "BIH" is not benign, because it would cause serious visual impairment and even blindness if the ICH and corresponding optical disk edema were not brought under control in time; in order to avoid the word "benign" causing neglect and misleading, and based on the fact that the etiology of intracranial pressure is unknown, for the first time the concept of the IIH was presented. Subsequent studies had also repeatedly confirmed that the IIH may lead to severe visual impairment or even blindness. In 1989, Corbett et al. [8] recommended that the disease should be described as IIH, while BIH started to be gradually abandoned. With the gradually increasing application of CT in clinical work, in 1985, Dandy's diagnostic criteria (1937) were revised by Smith [9] (the modified Dandy criteria), introducing CT into the criterion. Then the diagnostic criteria for IIH mainly include the following aspects: (1) symptoms and signs (headache, nausea, vomiting, transient blurred vision, optical disk edema); (2) no other focal neurological signs except the abducens nerve palsy; (3) increased CSF pressure without cytological or chemical abnormalities; and (4) imaging examination (mainly referring to CT) indicating that the cerebral ventricular volume is normal or decreased, with bilateral symmetry. In view of the continuous development of MRI and MRV in application and clinical job, as well as the deepening understanding for the IIH and other related diseases causing ICH, Friedman and Jacobson in 2002 [10] reinterpreted the modified Dandy criteria, stressing to pay attention to other related diseases causing ICH except the cerebral venous sinus thrombosis (CVST) and cause, with the specific content being discussed below.

4.1.3 Epidemiology

The incidence of IIH in the general population is estimated to be 0.9/100000. Among young women aged 15 to 44, the incidence is approximately 3.5 per 100,000. Among young obese women aged 20 to 44 who are more than 20% over their ideal body weight, the incidence was about 19.3 per 100,000, while atypical cases could also occur in men, children, and elderly people [11]. In the prepubertal cohort, the incidence of IIH is hardly related to obesity and gender, and the proportion of men and women is roughly equal, and thus the characteristic as high occurrence in women and obese people is not found. The IIH is very rare in people over 45 years old [17]. From the above data, it can be seen that the IIH is most prevalent in obese women in reproductive age, with around 1:8 as the ratio of males to females. Following the rising prevalence of obesity around the world and the deepening understanding of the IIH, the incidence of IIH is supposed to continue to rise.

4.1.4 Pathogenesis

Since Quincke first detailed the IIH over a hundred years in 1893, the specific pathogenesis of IIH has not yet been known, although the researchers have proposed multiple hypotheses to try to clarify the pathogenesis of it. Any pathogenesis must be able to explain the following points: (1) its favorite population as young, obese women; (2) no obvious enlargement of the cerebral ventricle in imaging examination; (3) relation between IIH and various drugs, such as tetracyclines, vitamin A, and its derivatives; and (4) relation between IIH and a variety of systemic diseases, such as polycystic ovary syndrome and sleep apnea. The first two points are the most critical and important.

Although various theories have been emerging to try to explain the pathogenesis of IIH, there is no strong evidence for any of them, and no theory can explain the pathogenesis of IIH alone. There are several theories that mainly focus on the following four aspects: "disorders in CSF circulation dynamics, sex hormone secretion disorders, obesity and endocrine function of adipose tissues, and blood coagulation dysfunction."

4.1.4.1 Disorders in CSF Circulation Dynamics

It mainly includes three aspects, i.e., excessive cerebrospinal fluid, backflow of cerebrospinal fluid or resorption disorders, and pressure elevation of intracranial vein sinus. Excessive cerebrospinal fluid in this hypothesis has been refuted by a large number of studies; in patients with IIH we did not find evidence for an increased secretion of cerebrospinal fluid, and the excessive cerebrospinal fluid (e.g., choroid plexus papilloma) can cause hydrocephalus and expanded cerebral ventricle. "Cerebrospinal fluid reflux disorder" and "elevated intravenous pressure in the intracranial sinus stenosis" are supported by more and more researches and evidences, while the causal relationship between the two has been controversial. At present a large number of studies have shown that intracranial venous sinus stenosis (especially for the unilateral or bilateral transverse sinus stenosis, the exclusion of intracranial venous sinus thrombosis should be noted) increases the intracranial venous pressure, resulting in reduced arachnoid granulations of cerebrospinal fluid resorption, occurrence of the cerebrospinal fluid backflow obstacles, then narrowing of the vein sinus, and finally formation of a vicious circle [12]. Any damage to this cycle in some patients, such as lumbar puncture or cerebrospinal fluid shunt, can make a longer relief of ICH symptoms, which has been further confirmed (Fig. 4.1).

However, just as the figure here reveals, the problem whether the venous sinus stenosis causes ICH or ICH causes sinus stenosis is still controversial and needs further research.

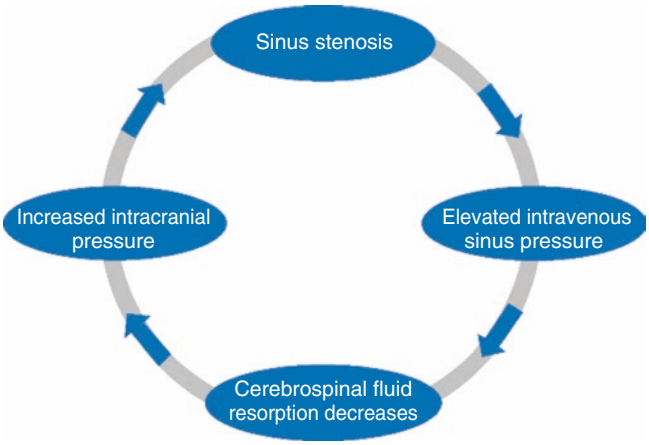

Fig. 4.1 Disorder of cerebrospinal fluid circulatory dynamics

4.1.4.2 Sex Hormone Imbalance

IIH tends to occur in young female, and many patients with IIH have a history of menstrual disorder; moreover, there are some case reports that relate IIH to the use of oral contraceptives and polycystic ovary syndrome, which arouses the researchers' interest in the role of estrogen in the pathogenesis of IIH. Donaldson et al., the scholars, found that the estrogen concentration increased in six obese female patients, and five cases in the control group did not change; thus they speculated that estrogen might influence the producing of choroid plexus cerebrospinal fluid in some way, and thus caused the ICH [13]. Other studies had found similar changes, further supporting the claim. However, in 15 cases of IIH patients, Soelberg et al. did not find changes in estrogen concentration of IIH patients, although 12 cases among them were obese women [14]. Though controversial, and concrete connections are unknown, the role of sex hormone secretion disorder in the pathogenesis of IIH still cannot be ruled out, while there shall be more massive researches including more patients to answer this question.

4.1.4.3 Obesity and the Endocrine Function of Adipose Tissue

Obesity has long been known to be closely related to IIH, and a series of studies have also certified and supported it. In a prospective study of 34 patients (31 women and 3 men), Rowe and other scholars found that 94% of patients were overweight (body mass index, BMI >26 kg/m^2), and 70.5% were obese (BMI >30 kg/m^2) [15]. In their study, Galvin and other scholars found that 90% of women were obese, and all five men were obese [16]. Recent weight gain is a widespread phenomenon in newly diagnosed IIH patients, and many studies have further confirmed this. According to Sugerman et al., accumulation of adipose tissues in the abdominal cavity because of obesity causes the intra-abdominal pressure to increase, then the diaphragm is elevated, thus the intrathoracic pressure

increases, and the internal pressure of the cardiac vein increases, which finally leads to ICH [17]. Meanwhile, Kesler et al. showed that in IIH fat tends to preferentially accumulate in the lower body relative to other obese women of the same range, whereas common diseases such as hypertension and diabetes are linked to upper body adiposity [18]; this makes the view of Sugerman et al. hard to gain a foothold. Recent researches have suggested that the generation and secretion of various cytokines and hormones in adipose tissues play an important role in the development of IIH [19]. The most critical, important, and the most well studied of all cytokines and hormones is leptin, a hormone involved in energy metabolism. Studies have shown that CSF concentrations of leptin in patients with IIH were indeed higher compared with those of the control group [20]; however, there were also studies which did not find this change [21], so which role leptin plays and how it plays in the occurrence of IIH are still unknown, but there is actually a relationship between leptin resistance of hypothalamus and obesity.

4.1.4.4 Abnormal Coagulation Function

In patients with potential thrombophilia, microthrombus can be found in intracranial vein sinus, which affects the arachnoid granulation resorption of cerebrospinal fluid, resulting in ICH, yet which is hard to be identified in imaging examination [22]; for this kind of patients we should pay attention to differentiate between it and intracranial venous sinus thrombosis. And studies have shown that these patients are more common [23] in people with a normal or lower BMI.

4.1.4.5 Other Related Conditions or Diseases

In addition to the preference for obese women in reproductive age, IIH had been related to vitamin A or its derivatives, which is also widely studied and concerned. The resorption of CSF by arachnoid granules is affected through some mechanism for metabolic abnormalities or poisoning of vitamin A, thus leading to ICH. And studies have shown that the concentration of retinol and retinol-binding protein in serum and CSF of some patients with IIH was increased indeed [22]. The relationship between IIH and other drugs such as tetracycline drugs, oral contraceptives, diseases as systemic lupus erythematosus (SLE), polycystic ovary syndrome, and sleep apnea syndrome is constantly seen in literatures, while the exact mechanism with details is still not clear, which needs further study and validation.

4.1.5 Clinical Manifestation

4.1.5.1 Symptoms

Headache

More than 90% of the patients are with moderate or severe headache, which is the most common symptom in complaints. It is usually a throbbing pain, sometimes accompanied by nausea, vomiting, photophobia (seen in more than 50% of patients), visual impairment, etc., which is heavier during the day, yet not persistent, and becomes heavier when the position changes, such as bending, lying down, or doing Valsalva maneuvers [24]. As the headache of this disease is nonspecific, and is similar to migraine or tension headache, it should be paid attention to for the identification.

Transient Visual Obscurations

More than 70% of patients have transient visual obscurations, which is also a common main complaint. It can occur in a single eye or both eye, which often lasts for a number of seconds, and is usually seen when standing, as the optic disk edema oppresses the optic nerve and causes its transient ischemia [24]. It is important to note that the frequency of the occurrence is not directly proportional to the degree of elevation of the optic disk edema or intracranial pressure, and the prognosis of the vision cannot be determined by it [25].

Pulsatile Tinnitus

About 60% of patients have pulsatile tinnitus, which is also the main complaint of some patients, while it is more specific than other symptoms [24]. It can be caused by unilateral or bilateral arterial pulsing in the ear, and can be alleviated by lumbar puncture or compression of the jugular vein.

Diplopia

Diplopia is another common symptom of IIH, seen in about 38% of patients [24]. There is usually binocular and horizontal diplopia, which is caused by unilateral or bilateral abducens paralysis and can be alleviated by lumbar puncture or other treatments reducing the intracranial pressure.

Visual Loss

Visual loss could be an initial symptom for a few patients, with blurred vision, scotomata (caused by the expansion of physiological blind spot), tunnel vision, etc. as the chief complaint, and even with complete loss of vision [24]. The speed of the deterioration of visual impairment has very big difference in different patients: the majority of patients can be stable for a long time, while a small number of patients, such as explosive IIH patients, would suffer complete loss of vision in a few days. Early onset of visual impairment often implies poor prognosis.

Other Symptoms

Other rare symptoms such as unilateral or bilateral retrobulbar pain, neck and shoulder pain, dizziness, ataxia, abnormal sensation, and facial paralysis can also occur. Other mental and cognitive symptoms such as anxiety, depression, attention-deficit disorder, and memory loss are also available, and they are increasingly being concerned by researchers.

4.1.5.2 Physical Signs and Auxiliary Examinations

Papilledema and Fundus Examination

Papilledema is the most important and symbolic sign of IIH, which is usually with bilateral symmetry, or occasionally unilateral or asymmetrical, while a very small number of patients have no optic disk edema. Early or mild papilledema is difficult to be found by the ordinary ophthalmoscope, and yet the stereoscopic fundus photography or fundus fluorescein angiography can be more sensitive to the edema. In addition, it is important to recognize the edema of the genuine papilledema and the pseudopapilledema, the latter of which is more commonly seen as optic disk drusen. Although visual impairment is associated with severe papilledema, the appearance of papilledema did not determine the prognosis of the vision.

Visual Loss and Visual Acuity Examination

The early stage of IIH usually does not affect visual acuity, color vision, and pupil function, so there is no chief complaint as visual impairment. In the early stage of papilledema, Snellen visual acuity of the patients was mostly normal or close to normal; thus, as it is not sensitive to the changes in vision, it could not be used as the sole indicator for evaluating the visual function. The contrast sensitivity is an early and sensitive indicator of visual impairment, which is better than visual acuity, but it is also less sensitive and practical than perimetry.

Visual Field Loss and Perimetry

Perimetry is the most sensitive and most common examination of IIH patients. Goldman perimetry or automated threshold perimetry is commonly used. Types usually seen of visual field defect are blind spot enlargement, inferonasal loss, and generalized constriction [24].

Ocular Motility Abnormalities

The abducens paralysis caused by ICH can lead to unilateral or bilateral external rectus paralysis, thus inducing binocular horizontal diplopia, and also esotropia. When various treatment measures make the intracranial pressure drop, the ocular motility abnormalities would be resolved.

4.1.6 Diagnosis

In 1937, Dandy established the IIH diagnostic criteria which had been modified for several times afterwards; with continuous development of MRI and MRV in clinical application, and further understanding of IIH and other related diseases that cause ICH, Friedman and Jacobson [10] elucidated the revised Dandy's criteria again in 2002, in order to make it more applicable to clinical use, and emphasized for noticing other relative diseases causing ICH except cerebral venous sinus thrombosis (CVST), with the following aspects mainly included: (1) only symptoms related to ICH or papilledema should be shown if there was any; (2) only signs related to ICH or papilledema should be manifested if there was any; (3) ICH (greater than 250 cm H_2O) is measured by lumbar puncture in the lateral decubitus position; (4) the components of cerebrospinal fluid are normal; (5) the brain MRI or enhanced CT scan of the typical patients shows no hydrocephalus, and intracranial occupying, structural or vascular lesion, while other patients should take cerebral MRI and MRV examination; (6) no other reasons for ICH have been confirmed.

4.1.7 Treatment

The main aim of the treatment is to relieve symptoms (especially headaches) and prevent visual impairment. For patients with minor papilledema yet without vision impairment, or within a relatively stable duration of vision acuity, close monitoring and conservative treatment (such as medication and weight loss) when necessary would be enough. Patients with severe or progressive visual impairment and who showed no improvement after being treated with active conservative treatment could be treated with surgery.

4.1.7.1 Weight Loss and Dietary Changes

Obesity and recent weight gain are definite risk factors for IIH; therefore, weight loss becomes a routine treatment for all obese patients. Kupersmith and some other scholars' studies had showed that 5–10% of the slight weight loss for patients with IIH could reduce the intracranial pressure and improve the papilledema [14], which was also supported by a series of other researchers' studies; however, weight loss takes a long time to reach and is difficult to maintain. A low-fat diet can reduce energy intake of a person and help lose weight; a low-salt diet can reduce the retention of sodium and water. Therefore, the combination of exercise or surgical weight loss and low-salt and low-fat diet can alleviate the symptoms of IIH patients to some extent.

4.1.7.2 Medications

1. Acetazolamide, a carbonic anhydrase inhibitor, is a drug for first-line treatment for IIH, which can reduce the generation of choroid plexus CSF, thereby reducing intracranial pressure and improving symptoms and signs. Studies by scholars such as Tomsak showed that acetazolamide is effective in about 75% of patients [15]; however, thus far there is lack of reliable, randomized, controlled trials to confirm its effectiveness. The recommended dosage is 500 mg, starting at twice a day, gradually increasing to the maximum dose of 2 g, twice daily. The common side effects include paraesthesia, parageusia (especially for

carbonated drinks), loss of appetite, kidney calculi, teratogenicity, etc. Parageusia is the most common side effect, and usually does not need drug withdrawal or special treatment; for pregnant women, remind them of the possible teratogenicity of this drug; methazolamide is used as an alternative medicine for patients who cannot tolerate the drug.

2. Topiramate is an antiepileptic drug which can also mildly inhibit the secretion of carbonic anhydrase and reduce the secretion of CSF from choroid plexus, and it is mainly used to treat headache, especially for IIH patients suffering from severe headache. Study by Celebisoy et al. showed that its efficacy in improving the symptoms of patients with mild-to-moderate IIH is comparable to that of acetazolamide [16], which could be considered as an alternative drug for those who cannot tolerate acetazolamide. Its main side effects are weight loss, kidney calculi, cognitive dysfunction, etc. It also has teratogenic effect, and should be cautiously applied for pregnant women; in rare cases, it can result in closed angular glaucoma and myopia, which are difficult to be differentiated from the visual impairment caused by IIH. The effect of topiramate on weight loss seems to indicate that it is more appropriate for treating IIH than other drugs, yet still clinical controlled trials with more extensive volume are needed for its validation.
3. Furosemide is a kind of loop diuretic, which has a powerful diuretic effect. It can also reduce the generation of CSF from choroid plexus, which can be used for the treatment of IIH, alone or combined with acetazolamide [17]. Its common side effect is hypokalemia; therefore, potassium supplement shall be noticed to be performed when applying it. Other side effects such as dehydration, rash, and tinnitus are rare.
4. The use of glucocorticoids for treating IIH has been controversial as it might lead to weight gain and fluid retention, which can aggravate the condition with intracranial pressure rebounding rapidly after reduction. The general recommendation is for emergency situations, as short-term application can improve the severe visual impairment to make time for further surgical treatment. It is not recommended for long-term use [18]. A large dose of methylprednisolone is usually chosen for administration as intravenous drip infusion.

4.1.7.3 Surgical Interventions

Despite active medical treatment, patients with progressive deterioration of visual impairment or explosive manifestations at the beginning of onset may undergo surgical treatment, but surgical treatment is not recommended for simple relief of headache. Until now the most common surgical methods are lumbar-peritoneal shunt (LPS), ventriculoperitoneal shunt (VPS), optic nerve sheath decompression (ONSF), and the controversial, newly developed intracranial venous sinus stenting, intending to reduce intracranial pressure and slow progress in visual impairment. Due to lack of related, randomized, controlled trials, it is impossible to distinguish between the superior and inferior; thus it is mainly determined by the personal preference and skill of the surgeon and the clinical manifestation of the patient for choosing the surgical method.

Repeated Lumbar Puncture

Lumbar puncture is a method that is not only diagnostic but also therapeutic, while a few patients can obtain symptom relief for a relatively longer term just by a diagnostic lumbar puncture. However, lumbar puncture operation has difficulty in obese patients, for whom there would be unbearable stinging pain from too many times of puncture, as well as complications such as low ICP tendency, leakage of CSF, and infection; thus it would not be applied as a conventional treatment means. At present, it is mainly a treatment means for the disease progression of pregnancy patients.

Bariatric Surgery

Surgical weight loss, especially for obese patients who failed to lose weight, can effectively alleviate the signs and symptoms of them [19], while it cannot be used in patients with acute progression, as it would take a while before it shows effects.

CSF Diversion

CSF diversion can reduce intracranial pressure, and make the signs and symptoms of patients with the IIH alleviate quickly. There are mainly two kinds of operative methods, VPS and LPS, with the true benefits of the two kinds of operative methods and long-term effect of CSF diversion not currently being determined, lacking validation and support by randomized, controlled, clinical trials and long-term follow-ups. At present, all the studies on VPS and LPS are retrospective, and both of them can relieve patients' headache and visual impairment, with respective advantages and disadvantages. As there is no increase of cerebral ventricular volume in patients with IIH, while stereotaxic VPS is always in need with difficulty in surgical operation and may cause serious complications such as epilepsy and intracranial hematoma, LPS is more favored in clinical application. Both types of surgery could have complications such as infection, obstruction or displacement of drainage tube, low ICP caused by excessive diversion, and repeated operations. Burgett et al. found in a retrospective study of 30 patients that symptoms and signs in 82% of the patients would be alleviated after CSF diversion, while 29% of them had symptoms and signs completely disappeared, yet with higher opportunity of repeated operations, which is 2.5 times/person on average [20]. Although the majority of patients have decreased intra-

cranial pressure and symptoms at early stage of postoperation, the long-term effects of CSF diversion are not very definite. Current data showed that CSF diversion could alleviate the visual impairment of 50% of patients in the first 2 years, and only 20% of patients had a headache. 51% of patients required reoperation, while 31% suffered from many times of operations [21], which suggested that surgery might not be the first choice for treating IIH, and only when medication and weight loss are ineffective, or visual impairment deteriorates rapidly, would it be considered.

Optic Nerve Sheath Fenestration (ONSF)

ONSF is usually considered to have cerebrospinal fluid pressure around the optic nerve reduced, optic nerve compression decreased, ischemia improved, papilledema lightened, and thus visual function improved on the operated side, while about 50% of the patients also improved on the opposite side. Its specific mechanism remains to be further elucidated. ONSF is performed more in some areas and medical centers, and data there showed that it stabilized and even improved 70–90% in patients with visual acuity; more importantly, compared with CSF diversion, ONSF has less complications and lower failure rate [22, 23], yet it might not ease the headache, and usually additional medication would be required for the treatment. Banta et al. assessed the efficacy and safety of ONSF, and for ONSF postoperative 156 eyes of 86 patients were retrospectively analyzed, and then it was found that visual acuity improved in 94% of patients, visual field improved or stabilized in 88% of patients, and vision-limited complications (such as blindness, temporary visual impairment) occurred only in less than 1% of the patients [22]. ONSF cannot be used for patients without papilledema and is usually used in patients with severe visual impairment or rapid progression.

Intracranial Venous Sinus Stenting

Intracranial venous sinus stenosis, especially the relationship between transverse sinus stenosis and IIH, makes intracranial venous sinus stenting become a new means for treating IIH, although there are some controversies. Model studies confirmed that stenting for venous sinus stenosis could reduce intravenous sinus pressure, increase CSF resorption, decrease intracranial pressure, and improve symptoms and signs, even though stenosis is caused by ICH. Higgins et al. used this method to treat 12 cases of intractable IIH, 7 of which were improved, and 5 did not show any obvious change [25]. Donnet et al. treated ten cases of IIH with this method, seven of which were improved, and the papilledema in all patients disappeared [26]. There are also many other cases reported in literatures, which generally showed positive results. Nonetheless, venous sinus stenting may lead to severe complications such as epidural hematoma, subdural hematoma, hearing loss, allergic reactions, and even death; moreover, the causal relationship between intracranial sinus stenosis and ICH is not clear, and thus its clinical application is limited, and would only be considered generally when the other treatment is invalid. The safety and long-term effect of it require more researches and observations to answer.

4.2 Conclusion

Many aspects of the IIH are ambiguous and unsolved, especially in terms of its pathogenesis. IIH favors the obese women of childbearing age. Although the incidence of it is relatively low at present, it would relatively increase with the spread of obesity worldwide. And it lacks large-scale, randomized, controlled clinical trials and long-term follow-up observation to guide the selection of the best treatment measures and the evaluation of long-term prognosis though there are a variety of treatment methods for this disease.

References

1. Quincke H. Meningitis serosa. Sammlung klinischer Vortrage Innere Medizin. 1893;67:655.
2. Nonne M. Uber Falle vom Symtomkomplex “Tumor Cerebri” mit Ausgang in Heilung “Pseudotumor Cerebri”. Deutsch Z Nervenheilkunde. 1904;27:169–216.
3. Symonds CP. Otitic hydrocephalus. Brain. 1931;54:55–71.
4. Dandy WE. Intracranial pressure without brain tumor: diagnosis and treatment. Ann Surg. 1937;106:492–513.
5. Foley J. Benign forms of intracranial hypertension: “toxic” and “otitic” hydrocephalus. Brain. 1955;78:1–41.
6. Buchheit WA, Burton C. Nomenclature in intracranial pressure. N Engl J Med. 1969;281(1):47.
7. Buchheit WA, Burton C, Haag B, Shaw D. Papilledema and idiopathic intracranial hypertension. N Engl J Med. 1969; 280(17):938–42.
8. Corbett JJ, Thompson HS. The rational management of idiopathic intracranial hypertension. Arch Neurol. 1989;46:1049–51.
9. Smith JL. Whence pseudotumor cerebri? J Clin Neuroophthalmol. 1985;5:55–6.
10. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology. 2002;59:1492–5.
11. Friedman DI. The pseudotumor cerebri syndrome. Neurol Clin. 2014;32:363–96.
12. Wakerley B, Tan M, Ting E. Idiopathic intracranial hypertension. Cephalalgia. 2015;35(3):248–61.
13. Wall M, George D. Idiopathic intracranial hypertension. A prospective study of 50 patients. Brain. 1991;114:155–80.
14. Kupersmith MJ, Gamell L, Turbin R, et al. Effects of weight loss on the course of idiopathic intracranial hypertension in women. Neurology. 1998;50:1094–8.
15. Tomsak RL, Niffenegger AS, Remler BF. Treatment of pseudotumor cerebri with Diamox (acetazolamide). J Clin Neuroophthalmol. 1988;18:93–8.
16. Celebisoy N, Gökc a F, Sirin H, et al. Treatment of idiopathic intracranial hypertension: Topiramate vs. acetazolamide, an open-label study. Acta Neurol Scand. 2007;116:322–7.
17. Schoeman JF. Childhood pseudotumor cerebri: clinical and intracranial pressure response to acetazolamide and furosemide treatment in a case series. J Child Neurol. 1994;9:130–4.

18. Liu GT, Glaser JS, Schatz N. High-dose methylprednisolone and acetazolamide for visual loss in pseudotumor cerebri. Am J Ophthalmol. 1994;118:88–96.
19. Fridley J, Foroozan R, Sherman V, et al. Bariatric surgery for the treatment of idiopathic intracranial hypertension. J Neurosurg. 2011;114:34–9.
20. Burgett RA, Purvin VA, Kawasaki A. Lumboperitoneal shunting for pseudotumor cerebri. Neurology. 1997;49:734–9.
21. Sinclair AJ, Kuruvath S, Sen D, et al. Is cerebrospinal fluid shunting in idiopathic intracranial hypertension worthwhile? A 10-year review. Cephalalgia. 2011;31:1627–33.
22. Banta JT, Farris BK. Pseudotumor cerebri and optic nerve sheath decompression. Ophthalmology. 2000;107:1907–12.
23. Spoor TC, McHenry JG. Long-term effectiveness of optic nerve sheath decompression for Pseudotumor cerebri. Arch Ophthalmol. 1993;111:632–5.
24. Bateman GA, Stevens SA, Stimpson J. A mathematical model of idiopathic intracranial hypertension incorporating increased arterial inflow and variable venous outflow collapsibility. J Neurosurg. 2009;110:446–56.
25. Higgins JN, Cousins C, Owler BK, et al. Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. J Neurol Neurosurg Psychiatry. 2003;74:1662–6.
26. Donnet A, Metellus P, Levrier O, et al. Endovascular treatment of idiopathic intracranial hypertension: clinical and radiologic outcome of 10 consecutive patients. Neurology. 2008;70:641–7.

The Relationship Between Sellar Tumors and Glaucoma

5

Yaxing Wang and Jian Wu

5.1 Introduction

Since sellar tumors are usually anatomically adjacent to optic nerves, optic chiasm, and optic tracts, tumor-induced compressive injury is common, which may cause eye diseases, such as papilledema and optic atrophy. Glaucoma refers to an optic neuropathy in which intraocular hypertension is the major risk factor; the typical clinical manifestations are optic disk changes and visual field defects. The clinical features of sellar tumors and glaucoma are distinct (especially in optic disk and visual field). The differential diagnosis between sellar tumors and glaucoma is challenging. From the perspective of ophthalmology, the main concern is how to avoid misdiagnosis of sellar tumors; meanwhile, from the perspective of neurosurgery, the clinicians should pay more attention to the identification of glaucoma in patients with sellar tumor. Both disciplines did not consider it as a whole. When considering from the perspective of integrated medicine (IM), we realize that there are a number of problems waiting for further discussion and practical solutions. To be more specific, is it a mere coincidence or inherent correlation that the glaucoma-like optic nerve neuropathy and sellar tumors appear simultaneously? If sellar tumor and glaucoma occur in one patient, then do they exactly belong to one disease or not? Utilizing the thinking way of IM, we will come to realize the limitation on clinic treatment in the past. Plus, it will initiate our wider ponder in this specific vicinity, such as whether it would result in susceptibility to glaucoma optic nerve damage that the sellar tumor has direct influence on anterior optic path. Or could exploration in the deeper way be developed as whether there is an underlying mechanism that the sellar tumor will result in glaucoma, and vice versa? Meanwhile, when they both occur simultaneously, does it have inherent correlation with other areas, such as endocrinology and psychosomatic medicine? With utilizing the concepts from IM, the diagnosis and treatment for diseases would be more comprehensive and systematic.

Intracranial tumor, especially sellar tumor, may lead to compressive injury on optic chiasm and optic tracts owing to the anatomical location, and cause eye diseases such as papilledema and optic atrophy. The optic atrophy can be commonly observed for the pale optic disk and moderate-to-severe atrophy of the retinal nerve fiber layer.

Glaucoma, a type of disease characterized by intraocular hypertension, can lead to visual loss, and it has characteristic optic disk changes and visual field defects. Owing to its high rate of morbidity and blinding and since the pathogenesis remains unknown, it has always been the hot spot of the optical study [1]. Thus far, the hypotheses of glaucoma occurrence include pressure theory, blood flow theory, and systemic disease theory. However, none of these enable to offer a plausible explanation for the pathogenesis of glaucoma.

The morphologic change of glaucoma is the mainstay for diagnosis of glaucoma. Characteristic lesions include loss of neuroretinal rim, advanced glaucomatous optic disk cupping, neuroretinal rim hemorrhage, peripapillary choroidal atrophy (PPCA), retinal arteriolar narrowing, local defects of retinal nerve fiber layer, and so on. In most patients with optic neuropathies which are non-hereditary and non-glaucomatous, optic disk may be pale while no comorbidity characteristic changes, neither advanced optic disk cupping nor development as well as expansion of choroidal atrophy. Due to the damages both located in the retinal nerve fiber layer, glaucoma and non-glaucoma optic neuropathies might have certain similarities in the latter period. For instance, the

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_5

appearance of waxy pallor of the optic nerve head is the result of chronic glaucoma development at certain stage, whereas, non-glaucoma optic atrophy may also have the onset of advanced optic disk cupping in late stage [2]. The key to the identification of them is to determine the primary and secondary lesions, i.e., distinguish between waxy pallor of the optic nerve head and advanced optic disk cupping to find which of them is the major characteristic; at the same time, it is required to observe whether retinal nerve fiber layer defects are in accordance with the neuroretinal rim changes. It is generally not difficult to distinguish when analyzing carefully and grasping the detailed features.

However, there are some patients with intracranial tumor who may occasionally have glaucoma-like fundus changes in clinical practices. It is reported in several researches that sellar tumors and "normal-tension glaucoma" may combinedly occur [3, 4]. Because of the relatively definite morphologic differences between compressive optic atrophy and glaucoma, we consider whether sellar tumors could result in other types of optic nerve damage apart from the compressive harm. Thus, the research was devised as follows [5].

This retrospective study enrolled patients with sellar tumor in Beijing Tiantan Hospital. Data were collected from July 2008 to December 2009. There were 263 females and 238 males, with a mean age of 40.2 ± 15.7 years. All patients underwent a cranial MRI, CT, and other radiological examinations, as well as a routine postoperative pathological examination. Patients routinely received ophthalmologic examination, visual field testing, and fundus photography before the operation.

Categorized as to tumor pathology, there were 336 cases of pituitary adenoma, 32 cases of sellar meningioma, 89 cases of craniopharyngioma, 9 cases of chiasmal glioma, and 35 cases of other sellar tumors. On the basis of location, there were intrasellar tumors (143 cases, 28.5%), parasellar tumors (36 cases, 7.2%), suprasellar tumors (321 cases, 64.1%), and retrosellar tumors (1 case, 0.2%). The measured mean length, width, and height were 23.1 mm ± 11.0 mm, 23.8 mm ± 10.7 mm, and 24.3 mm ± 11.7 mm, respectively.

The morphological criteria for the diagnosis of glaucoma are that rim shapes are not consistent with the ISNT (inferior-superior-nasal-temporal rule) theory [6], while visual field damage standards took the glaucoma visual field damage standards developed by Hodapp et al. [7]. As the intraocular pressure data is incomplete, it was not regarded as a diagnostic indicator. The diagnosis of glaucoma in the sellar tumor group is showed in Fig. 5.1.

The control group was selected from the Beijing Eye Study (BES), a total of 454 people and the average age of 40.9 ± 0.8 years old [8]. The double-blinded qualitative and quantitative analysis was then performed on the fundus photographs of the tumor group (i.e., the study group) and the normal eye group in BES (i.e., the control group).

The vertical cup disk ratio (VCDR) was 0.47 ± 0.14 in the tumor group and 0.44 ± 0.12 in the control group, which was significantly lower than that in the study group ($p = 0.001$). According to the morphological definitions, a total of 34 patients in the study group had at least one eye diagnosed as glaucoma (morbidity: 6.8 ± 1.1%), which was significantly higher than the morbidity of the control group (1.3 ± 0.5%) ($p < 0.001$). The VCDR of the 34 cases of glaucoma eyes were 0.63 ± 0.16 in right eyes and 0.67 ± 0.14 in left eyes, which were significantly higher than those in the control group (0.44 ± 0.12) ($p < 0.001$).

The morbidity of glaucoma was 12.9 ± 6.1% (95% CI: 1.0–24.0%) in the meningioma group, 7.8 ± 1.5% (95% CI: 4.9–10.6%) in the pituitary tumor group, and 4.5 ± 2.2% (95% CI: 0.2–8.8%) in the craniopharyngioma group (Table 5.1).

There was a significant positive correlation between glaucoma and age ($p = 0.002$), tumor length ($p = 0.02$), and width ($p < 0.001$) by univariate analysis. It was also associated with tumor location: the morbidity of glaucoma in patients with suprasellar/parasellar tumors was significantly higher than in intrasellar tumors ($p = 0.010$ and $p = 0.001$). In this study, glaucoma was found only in patients with meningiomas, pituitary tumors, and craniopharyngioma. In this study, glaucoma was found only in meningiomas, pituitary tumors, and craniopharyngioma patients. After multivariate regression analysis, glaucoma was found to be significantly associated with age ($p = 0.001$), tumor location ($p = 0.016$), and tumor width ($p = 0.002$). It seems to be more likely to have glaucoma-like fundus performance when the parasellar tumors are greater and closer to the intracranial end of optic canal.

Then, further analysis was done on the parapapillary atrophy [9]. Atrophy is a morphological structure independent of glaucoma and is one of the signs of glaucoma diagnosis and progression. In the glaucoma identified in the sellar tumor group, 79.4% of their eyes had atrophy and only 49.1% in the control group; thus the difference was significant. In addition, there were significant differences in the width, extent, and area of atrophy between the two groups, as the atrophy of glaucoma group was significantly larger than that of the control group. The width and area of the atrophy were analyzed, and it was found that it correlated with tumor width significantly and positively.

This series of studies have confirmed that the morbidity of glaucoma in patients with sellar tumor was higher than that of the normal population from the subjective judgments, objective indicators of measurement, and other aspects. However, what is the mechanism for the occurrence of such a glaucoma?

Presumably the reason is firstly that some of the larger tumors oppress intracranial optic nerve and optic chiasm and

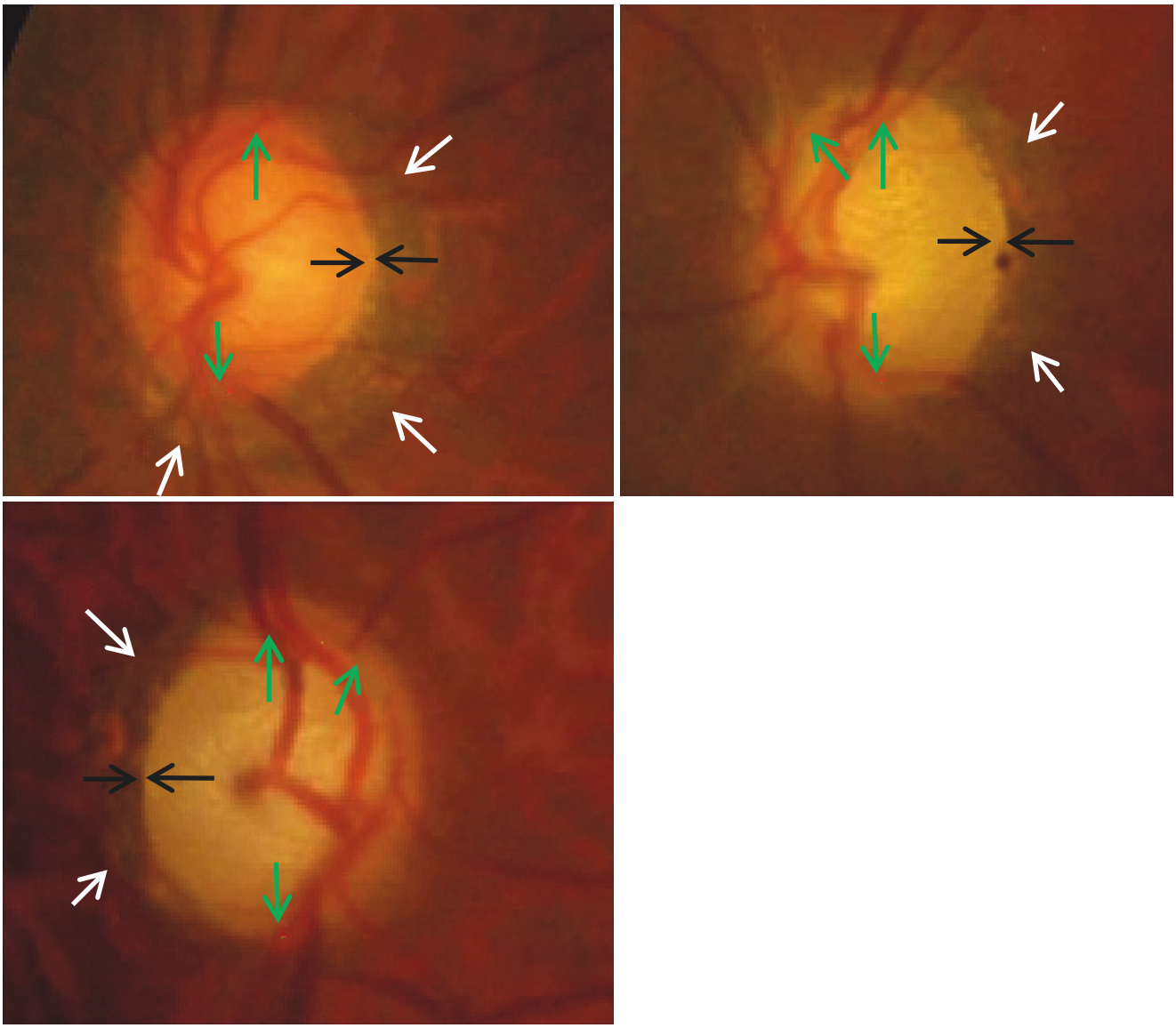

Fig. 5.1 Glaucoma fundus images in the sellar tumor diagnosis group. Green arrow: narrowing of the edge of the disk. White arrow: Shrink arc. Black arrow: Scleral ring. Reproduced with permission from Wang Ya X, Xu Liang, Lu Wen et al. Parapapillary atrophy in patients with intracranial tumours. Acta Ophthalmol, 2013, 91: 521–5

Table 5.1 Sellar tumor location classification and the prevalence of glaucoma (morphological diagnosis)

Type	Number	Ratio	Age	Glaucoma n	Prevalence (%)	Unreadable
Intrasellar tumor	143	28.5	42.4 ± 12.0	1	0.7 ± 0.7	2
Suprasellar tumor	321	64.1	38.5 ± 17.0	29	9.0 ± 1.6	0
Parasellar tumor	36	7.2	46.5 ± 14.1	4	11.4 ± 5.5	1
Posterior saddle tumor	1	0.2	51	0		0
Total	501	100.0	40.2 ± 15.7	34	6.9 ± 1.1	3

hinder the normal circulation of the subarachnoid cerebrospinal fluid, and as a result cerebrospinal fluid cannot enter the optic canal and orbital cavity. Normally, the retrobulbar lamina cribrosa is balanced between the pressure from the intracranial cerebrospinal fluid and the intraocular pressure, and the optic disk does not develop glaucoma-like pits. If the optic nerve subarachnoid cerebrospinal fluid circulation is blocked, the pressure of cerebrospinal fluid cannot be passed to the retrobulbar part; thus there would be difference between intraocular pressure and retrobulbar cerebrospinal fluid pressure; that is, increased trans-lamina cribrosa pressure leads to optic disk pitting, causing glaucoma-like optic

neuropathy. The change in pressure is equivalent to the increase of intraocular pressure while normal cerebrospinal fluid pressure remaining. It was reported that a large carotid ophthalmic aneurysm oppression on the optic nerve and optic canal will lead to the same glaucoma-like optic neuropathic changes [10]. This hypothesis is now indirectly confirmed by some clinical studies. Recently, some scholars found that intracranial CSF pressure is relatively low in patients with normal-tension glaucoma [11]. Tokumaru et al. reported the widening of subarachnoid space 26 months after pituitary tumor surgery, indirectly demonstrating that tumor bodies may block the circulation of retrobulbar cerebrospinal fluid [12]. The results of this study further support the hypothesis that retrobulbar cerebrospinal fluid pressure leads to normal-tension glaucoma.

In addition, there are other possible mechanisms, such as retrograde degeneration from the optic chiasma to the optic disk, which alter the integrity of the optic papilla and cause glaucoma-like changes. The direct compression from the tumor may cause optic nerve fiber damage and, on this basis, glaucoma-like optic nerve changes are prone to occur.

There are some limitations in this study. First, this study is a retrospective study, with retrospective bias; second, the factor of intraocular pressure was not taken into account, and thus the possibility of high intraocular pressure in the tumor group cannot be ruled out; in addition, this study only carried out a correlation and comparison, without further researching on the mechanism.

In conclusion, this study found that the morbidity of glaucoma-like lesions in patients with suprasellar and parasellar tumors was significantly higher than that in a population-based control group. The morbidity of glaucoma is significantly related to the location and size of the tumor. It seems to be more likely to have glaucoma-like fundus performance when the parasellar tumors are greater and closer to the intracranial end of optic canal. The size of atrophy in tumor patients with glaucoma is positively related to tumor width. Thus, we believe that apart from the sellar tumor presenting direct compression of the optic nerve, resulting in a typical optic nerve atrophy, there is another mechanism that may cause glaucoma-like optic neuropathy. Clinically, for patients with normal-tension glaucoma, doctors should also be aware of whether intracranial lesions are complicated or not.

References

1. Teng CC, De Moraes CG, et al. JM ß-zone parapapillary atrophy and the velocity of glaucoma progression. Ophthalmology. 2010;117:909–15.
2. Jonas JB, Xu L. Parapapillary chorioretinal atrophy in normal-pressure glaucoma. Am J Ophthalmol. 1993;115:501–5.
3. Ahmed II, Feldman F, Kucharczyk W, et al. Neuroradiologic screening in normal-pressure glaucoma: study results and literature review. J Glaucoma. 2002;11:279–86.
4. Blumenthal EZ, Girkin CA, Dotan S. Glaucomatous-like cupping associated with slow-growing supra-sellar intracranial lesions. J Neuroophthalmol. 2006;30:111–5.
5. Wang YX, Xu L, Yang H, et al. Prevalence of glaucoma in North China. The Beijing Eye Study. Am Ophthalmol. 2010;150:917–24.
6. Qu YZ, Wang YX, Xu L, et al. Glaucoma like optic neuropathy in patients with intracranial tumours. Acta Ophthalmol. 2011;89:e428–33.
7. Wang YX, Xu L, Lu W, et al. Parapapillary atrophy in patients with intracranial tumours. Acta Ophthalmol. 2013;91:521–5.
8. Jacobson DM. Symptomatic compression of the optic nerve by the carotid artery: clinical profile of 18 patients with 24 affected eyes identified by magnetic resonance imaging. Ophthalmology. 1999;106:1994–2004.
9. Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma. A prospective study. Ophthalmology. 2010;117:259–66.
10. Tokumaru AM, Sakata I, Terada H, et al. Optic nerve hyperintensity on T2-weighted images among patients with pituitary macroadenoma: correlation with visual impairment. AJNR Am J Neuroradiol. 2006;27:250–4.

Glaucomatous Injury of Central Nerve System

6

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6.1 Introduction

Glaucoma is generally considered to be a disease limited to the eye resulting from characteristic changes to the optic nerve head and corresponding visual field defects caused by elevated intraocular pressure. Therefore, the target of therapies has always been reducing intraocular pressure, supplemented by optic nerve nutritional therapy. Although glaucoma has long been recognized as an optic nerve disease, the study on the glaucomatous pathology merely reached the extracranial segment of the optic nerve, ignoring an important feature of the optic nerve, which constitutes the central nervous system (CNS). Hence, some unexplained problems in clinical practices remained, such as why the visual field impairment and optic nerve damage continue to progress with well-controlled IOP. In this section, the local optic neuropathy caused by glaucoma has been considered as part of disturbance of the whole CNS, and the concept of "integration" is introduced to discuss the characteristics of glaucomatous injury from the entire visual pathway perspective: Glaucoma is a disease impairing the whole visual pathway, which affects not only the optic ganglion cells, but also leads to the destruction of the superior neurons, which might be damaged even earlier than the ganglion cells in glaucoma; the function of not only pathway for form sense but also other sensory pathways would be affected, while the damage by glaucoma may also be associated with the reshape of the structure and function of the cortex. This section enables readers to rediscover the seemingly localized disease, glaucoma, from the integrative perspective of the visual pathway and provides new insights into the diagnosis and treatment of glaucoma in a more comprehensive way.

The understanding of glaucoma is limited to the aqueous circulation disorders and optic nerve impairment. With the in-depth study of glaucoma and visual science, and the development of the interdisciplinary of ophthalmology neurosciences, new problems of interdisciplinary science have been brought forward, namely whether glaucoma is a disease limited to optic nerve or not; whether it is a disease confined to the eyes but affecting the whole visual pathway or not; or whether it would be just a special type of CNS disease with ocular presentations or not. These problems have so far been inconclusive; however, it is reasonable to believe that to classify glaucoma as a neurodegenerative disease of the eye and brain would be of great significance for understanding its pathogenesis, establishing comprehensive treatment system and preventing blindness from glaucoma.

6.1.1 Glaucomatous Injuries Involving the Entire Optic Pathway

With the in-depth of glaucoma research and neuroimaging advancement, increasing evidence shows that the glaucomatous injury is not only confined to the retina, but also the whole visual pathway including optic nerve, optic chiasma, optic tract, lateral geniculate body, optic radiation, and occipital visual cortex.

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https://doi.org/10.1007/978-981-13-7896-6_6

6.1.1.1 Evidence from Animal Experiment

In rodent and primate glaucomatous animal models, sustained elevated intraocular pressure can not only lead to RGC loss, but also cause atrophy and loss of neurons at the corresponding layer in lateral geniculate nucleus (LGN) which receives projection from the injured optic fiber, manifested as the decrease of the cross-sectional area of the cells and the decrease of cell density [1]. Meanwhile, the dendrites of each layer of LGN neurons would be shortened and thickened, and the structure disordered, along with marked decrease of complexity of dendrites and the range of dendritic fields [2]. Diffuse glial proliferation could also be observed in the same region [3]. Less activities of cytochrome oxidases [4] and choline levels were observed, the content of other metabolites in ocular dominance columns of visual cortex and LGN layer which receives visual information input of damaged eye all declined, and the expression and distribution of synaptic plasticity-associated proteins significantly changed, such as growth-associated protein 43 (GAP43). Changes in CNS neurons, glial cells, and protein expression are accompanied by changes in visual system function. The reaction of LGN neurons in different stimulation conditions was studied by using the extracellular record in the cat's acute elevated intraocular pressure model, and the reaction of different components in different types of LGN cells and receptive field was found to be significantly decreased after the IOP elevated, which also had different impact on the X and Y cells, the center and peripheral mechanisms, and the cell dispension reaction on peak and count [5]. It was also found that the neural reactivity of the visual cortex of the monkeys with monocular ocular hypertension was significantly decreased when stimulated using positron-emission tomography (PET).

6.1.1.2 Pathological Study of Human Glaucoma

Apart from the data from animal experiments, observation on human patients with glaucoma showed similar results. Gupta et al. performed a pathological study of brain samples from a patient with glaucoma, and found that the thickness of LGN and visual cortex was significantly thinner in the patient than in the normal subjects; the cross-sectional area of neurons became smaller, showing small ball shape which is different from normal long spindle shape [6].

6.1.1.3 In Vivo Study on Human Glaucoma Patients

For patients with glaucoma, the in vivo MRI method results showed that, compared with normal age-matched controls, bilateral LGN height of glaucoma patients was significantly decreased while volume was significantly reduced; there is a close relationship between LGN change and cup disc ratio and retinal nerve fiber layer thickness of patients [7]. Diffusion tensor-MRI (DT-MRI) found that the mean diffusivity (MD) of optic nerve, optic tract, and optic radiation in glaucoma patients were significantly higher than those in normal controls, while the fractional anisotropy (FA) significantly decreased, and there was a linear correlation between these changes and the stages of glaucoma, the thickness of the retinal nerve fiber layer, and the structural parameters of the optic disc, suggesting that damage to the normal structure and walking of the axons in optic nerve, optic tract, and optic radiation of glaucoma patients were consistent with the severity of the disease [8].

6.1.2 The Superior Neural Damaged No Later than RGCs

6.1.2.1 Evidence from Animal Experiment

When IOP is elevated in the monkey eye, RGC death occurs with characteristic optic nerve head changes,[40] similar to human glaucoma.[41] RGC atrophy[51] and loss[39] are well described in this experimental primate model of glaucoma. Marked changes in RGC axons are also noted behind the globe in this model.[56] In the LGN, neuropathological examination reveals marked degenerative changes including neuron shrinkage and loss. There is evidence that the damage to LGN neurons may be synchronized with RGC atrophy, or even earlier. When IOP is elevated in the rat eye 3 days later, RGC atrophy and loss and marked changes in LGN and superior colliculus neurons were observed. Crish et al. found that the earliest manifestation of visual pathway damage in rodent models of spontaneous glaucoma was the obstructed anterograde axonal transport of the distal RGC axons, i.e., anomalies of exchange for LGN receiving material and information from the RGC projection area. This change occurs before the degeneration of RGC axons and presynaptic structural, which would develop from the distal to the proximal end, and eventually affect the retina. As a result, the researchers boldly concluded that the initial injury of glaucoma may be the brain, but not the retina [9].

6.1.2.2 Glaucoma Patient Study

Using BOLD fMRI, it is found that the visual response of the corresponding visual cortex to visual stimuli has been attenuated in glaucoma patients with normal central vision [10].

6.1.3 Damages in Both Pathway for Form Sense and Other Sensory Pathways

Animal experiments have found that high intraocular pressure has an effect on the structure and function of RGCs which contain melanopsin. Chiquet et al. found in the mouse glaucoma model that, besides the damage to the entire visual pathway, there is also an impairment of suprachiasmatic

nucleus, associated with synchronization of circadian rhythms and this human nucleus, which may arise from transsynaptic damage induced by RGC death conducting to the nucleus [11]. However, the clinical experiment found that the circadian rhythm of glaucoma patients was significantly abnormal compared with that of normal people.

6.1.4 Brain Atrophy and Remodeling of the Structure and Function of the Cerebral Cortex

Recent studies have compared the volume of gray matter in different regions of the brain between glaucoma patients and normal people via MRI, which showed that in patients with glaucoma, the volume of gray matter in bilateral lingual gyrus, calcarine gyrus, postcentral gyrus, superior frontal gyrus, inferior frontal gyrus, right cuneus, right midoccipital gyrus, left paracentral lobule, and right supramarginal gyrus decreased more significantly than normal subjects in the control group, and the volume of gray matter in bilateral midtemporal gyrus, angular gyrus, inferior parietal lobe and left superior parietal gyrus, precuneus, and midoccipital was significantly larger than that of the normal controls [12]. Another group studied the gray matter density of the whole brain in glaucoma patients with the morphological analysis based on volume element, and found that there was no change in gray matter density in early glaucoma patients, while in the progressive and advanced glaucoma patients the gray matter density of bilateral primary visual cortex (BA17 and BA18), bilateral paracentral lobule (BA5), right precentral gyrus (BA6), right midfrontal gyrus (BA9), right inferior temporal gyrus (BA20), right angular gyrus (BA39), left precuneus (BA7), left middle temporal gyrus (BA21), and superior temporal gyrus (BA22) decreased more significantly than normal subjects. Meanwhile, the gray matter density of BA39 region increased significantly [13]. These results suggested that the damage to CNS neurons in glaucoma patients had not only affected the visual cortex, but also induced the remodeling of cortical structures and functions [14].

6.2 Conclusion

In summary, glaucomatous disturbance impairs the whole visual pathway, while the superior neuron damage is a relatively early phenomenon, even before the ganglion cell injury. Glaucomatous damage affects not only form perception pathway, but also sensory pathways. In addition, optic cortex atrophy resulting from glaucoma may also simultaneously remodel the structure and function of the cortex. The contribution of visual pathway changes to glaucomatous disease should be taken into account as we strive for novel approaches to diagnose and monitor disease, and understand glaucoma from the holistic perspective.

References

1. Yucel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. Prog Retin Eye Res. 2003;22(4):465–81.
2. Gupta N, Ly T, Zhang Q, et al. Chronic ocular hypertension induces dendrite pathology in the lateral geniculate nucleus of the brain. Exp Eye Res. 2007;84(1):176–84.
3. Sasaoka M, Nakamura K, Shimazawa M, et al. Changes in visual fields and lateral geniculate nucleus in monkey laser-induced high intraocular pressure model. Exp Eye Res. 2008;86(5):770–82.
4. Crawford ML, Harwerth RS, Smith EL 3rd, et al. Experimental glaucoma in primates: changes in cytochrome oxidase blobs in V1 cortex. Invest Ophthalmol Vis Sci. 2001;42(2):358–264.
5. Liming T, Nan Z, Xiang Y, et al. Influence of short-term intraocular pressure elevation on receptive field of cat's dorsal lateral geniculate nucleus. Chin Sci Bull. 2004;49(10):961–4.
6. Imamura K, Onoe H, Shimazawa M, et al. Molecular imaging reveals unique degenerative changes in experimental glaucoma. Neuroreport. 2009;20(2):139–44.
7. Gupta N, Ang LC, Noel de Tilly L, et al. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. Br J Ophthalmol. 2006;90(6):674–8.
8. Hernowo AT, Boucard CC, Jansonius NM, et al. Automated morphometry of the visual pathway in primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2011;52(5):2758–66.
9. Zhang S, Wang H, Lu Q, et al. Detection of early neuron degeneration and accompanying glial responses in the visual pathway in a rat model of acute intraocular hypertension. Brain Res. 2009;1303:131–43.
10. Qing GP, Wang NL. Functional MRI signal changes in primary visual cortex corresponding to the central normal visual field of patients with primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2010;51(9):4627–33.
11. Chiquet C, Drouyer E, Woldemussie E, et al. Consequences of glaucoma on circadian and central visual systems. J Fr Ophtalmol. 2006;29(7):847–51.
12. Chen Z, Lin F, Wang J, et al. Diffusion tensor magnetic resonance imaging reveals visual pathway damage that correlates with clinical severity in glaucoma. Clin Exp Ophthalmol. 2013;41(1):43–9.
13. Chen WW, Wang N, Cai S, et al. Structural brain abnormalities in patients with primary open-angle glaucoma: a study with 3T MR imaging. Invest Ophthalmol Vis Sci. 2013;54(1):545–54.
14. Li C, Cai P, Shi L, et al. Voxel-based morphometry of the visual-related cortex in primary open angle glaucoma. Curr Eye Res. 2012;37(9):794–802.

7 Glaucomatous Injury of Central Nerve System: The Role of Neuroimaging Technology in the Understanding of Disease

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7.1 Introduction

Understanding glaucoma is an endless process of continuous integration; for example glaucoma, which was firstly recognized to be a disease limited to the eye, has now been considered as a disease affecting the whole visual pathway with the characteristics of optic nerve injury in addition to corresponding visual field defects. Relevant contents have been elaborated in Chap. 6. In the process of overall integration, medical imaging technology plays an important role. There are varied approaches to study the characteristics and mechanisms of human diseases, especially with the booming progress of life science and modern molecular biology, so that the research can be carried out at the cellular level and molecular level. However, molecular biology has its insurmountable weakness—the limitation of the research object, as researchers can only inspect with clues from all kinds of animal models, autopsy of dead patients, and a small amount of local tissue from patients, and then infer to the human body. Only by morphological and functional observation in vivo could we understand the disease most authentically and effectively, which was barely possible for molecular biological method to achieve, while fortunately the imaging technology provides a means to realize the above purpose. This section discusses the role of neuroimaging techniques in understanding the process of damage to CNS by glaucoma, and it is hopefully that through reading this chapter, the readers would be able to understand advanced neuroimaging techniques used in ophthalmology nowadays; thus they would integrate the research methods of both molecular biology and imaging, the local part as the eye and the whole entire body, to provide new ideas and methods for further understanding glaucoma and other ophthalmic and nervous system diseases.

Glaucoma has been considered as a group of neurodegenerative diseases which could be mainly characterized by the loss of specific retinal ganglion cells and the visual field defects caused by this. However, with the developed research methods and deeper study of glaucoma, the point that glaucoma influences the whole visual pathway has been recognized by ophthalmology scholars. Neuroimaging techniques have played an important role in this process of cognition.

7.1.1 Glaucoma, a Disease Affecting Entire Visual Pathway

So far, the pathophysiology and pathogenesis of glaucoma have not been well understood. Pathologically elevated intraocular pressure is considered to be the most important risk factor for the development and progression of glaucoma [1]. In addition, perfusion abnormality of blood flow, immune response, toxicity of cellular excitability, and other changes are also closely related to glaucomatous optic nerve injury [2]. Studies on the pathogenesis of glaucoma directly affect the developing of effective clinical treatment method and

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_7

strategy. With the deepening of the exploration of visual science and the development of ophthalmology and other interdisciplinary subjects, increasing new breakthroughs and discoveries have been achieved on the understanding of the traditionally recognized eye disease, glaucoma [3–8]. More and more evidence shows that the glaucoma nerve damage is not only confined to the retina, but also affects the whole visual pathway including optic nerve, optic chiasma, optic tract, lateral geniculate body, optic radiation, and occipital visual cortex. In rodent and primate glaucoma models, sustained high intraocular pressure can cause atrophy and loss of neurons at the corresponding layer in lateral geniculate body (LGN) which receives projection from the injured optic fiber [9–14], and the diffuse proliferation response of glial cells is observed in the same region [15–17]. The activities of cytochrome oxidases [18–20] and choline levels and the content of other metabolites [21] in ocular dominance columns of visual cortex and LGN layer which receives visual information input of damaged eye all declined, and the expression and distribution of synaptic plasticity-associated proteins significantly changed, such as growth-associated protein 43 (GAP43) [22]. The pathological results of the brain specimen obtained from glaucoma patients are consistent with animal experiment: the thickness of LGN and visual cortex in glaucoma patients was significantly thinner than that of normal, with the atrophy of neurons [23]. The findings of these basic studies not only bring new insights into our previous knowledges on glaucoma, but also will make new innovation of the clinical practices accordingly. The study on damage to CNS by glaucoma and its related factors will help us understand the manifestation and mechanism of glaucomatous nerve injury more deeply and comprehensively, while more attention will be paid to the protection of the whole optic pathway and functional modulation may also lead to new breakthroughs in the treatment of glaucoma.

7.1.2 Role of Neuroimaging Technology in the Study on Damage to CNS by Glaucoma

The neuroimaging progress has made the study on glaucomatous damage to CNS in vivo possible. At present, there are extensive devices to detect the structure, function, metabolism, and perfusion of CNS, such as magnetic resonance imaging (MRI), CT, PET, and single-photon emission computed tomography (SPECT). In particular, with technological advancement, MRI could also perform diffusion tensor imaging, functional imaging, spectral analysis, perfusion imaging, and other functions based on the traditional scanning. These functions have further broadened the scope and area for application of MRI. With a variety of traditional imaging techniques and special imaging sequences, MRI can accurately observe the structure, metabolism, component, function, and blood perfusion of glaucomatous visual cortex, and may become an ideal tool for efficacy evaluation on new strategies for neural protection [24].

7.1.2.1 Magnetic Resonance Structural Imaging

Magnetic resonance imaging (MRI) is an imaging technique that uses nuclear signals generated by resonance in a magnetic field to reconstruct images, and it has more advantages in neuroimaging because of its noninvasiveness, reproducibility, and high spatial and temporal resolution. The results of structural magnetic resonance imaging (sMRI) showed that, compared with age-matched normal control group, the volume of optic nerve, optic chiasm, optic tract, LGN, and visual radiation decreased significantly in clinical glaucoma patients, and the height of LGN decreased significantly. There is a close relationship between changes of LGN and cup disc ratio as well as retinal nerve fiber layer thickness [25, 26]. The gray matter density of the anterior calcarine fissure of visual cortex in occipital lobe, which received corresponding optic nerve projection from the defect area of visual field, was locally decreased [27]. Recent studies used MRI to compare and analyze gray matter volumes in different areas of brain between glaucoma patients and normal subjects, and found that the gray matter volume of bilateral lingual gyrus, calcarine gyrus, postcentral gyrus, superior frontal gyrus, inferior frontal gyrus, right cuneate lobe, right inferior occipital gyrus, left paracentral lobule, and right supramarginal gyrus in patients with glaucoma decreased significantly than normal subjects in the control group, while the gray matter volume of middle temporal gyrus, inferior parietal gyrus, angular gyrus of bilateral side, superior parietal gyrus, anterior temporal lobe, and middle occipital gyrus of left side was significantly higher than that of the normal control group [28]. Another team used voxel-based morphological analysis to study gray matter density in the entire brain of glaucoma patients, and no changes in gray matter density were found in patients with early glaucoma, while in advanced stage of glaucoma patients the gray matter density of bilateral primary visual cortex (BA17 and BA18), bilateral paracentral lobule (BA5), right precentral gyrus (BA6), right middle frontal gyrus (BA9), right inferior temporal gyrus (BA20), right angular gyrus (BA39), left precuneus (BA7), left middle temporal gyrus (BA21), and superior temporal gyrus (BA22) decreased significantly compared with the normal control subjects; meanwhile, the gray matter density of BA39 area significantly increased [29]. These results suggested that the damage to CNS neurons in glaucoma patients had not only affected the visual cortex, but also induced the reconstruction of cortical structures and functions.

7.1.2.2 Diffusion-Tensor Magnetic Resonance Imaging (DT-MRI)

DT-MRI is a noninvasive technique for reconstructing axonal structures in 2 or 3 dimensions based on the dispersion of internal water molecules in axons. The increase in mean dispersion (MD) and fractional anisotropy (FA) was used to reflect the extent of axonal damage. Using this technique, the researchers found that MD of optic nerve, optic tract, and optic radiation increased significantly in glaucoma patients as compared with the normal control group, while FA was significantly lower. There was a linear correlation between these changes and the stage of glaucoma, the thickness of retinal nerve fiber layer, and the structure parameters of optic disc, suggesting that the normal structure and going of the optic nerve, optic tract, and axons of neurons in the optic radiation of glaucoma patients are consistent with the severity of the disease [30–35].

7.1.2.3 Proton Magnetic Resonance Spectroscopy (1H MRS)

Proton magnetic resonance spectroscopy (1H MRS) is the only noninvasive method to study the metabolism, biochemical changes, and quantitative analysis of human organs, and various micrometabolites can be detected in the interested area in vivo, such as the metabolite concentration of creatine (Cr), choline (Cho), lipids, inosine, gamma-aminobutyric acid (GABA), glutamic acid (Glu) and glutamine (Gln), taurine, lactic acid, and N-acetylaspartate (NAA) [36]. Among them, NAA mainly exists in neurons and is recognized as an internal marker of neurons, and its content reflects the functional status of neurons and the integrity of neurons [37]. Cho is mainly found in brain glia and is the major component of phospholipid biosynthesis, which is an index of myelination, cell metabolism, and gliosis, and also participates in the synthesis of neurotransmitter acetylcholine [38]. The spectral analysis of glaucoma model in rat visual cortex contents analyzed by Chan et al. found that the relative content of visual cortex cholinergic which receives the damaged optic fiber projection decreased obviously than normal visual cortex, while the content of glutamic acid is relatively increased [21]. This result is further validated in human glaucoma patients. Zhang et al. performed spectral analyses of calcarine fissure of lateral geniculate body and striate cortex in clinical glaucoma patients. The results showed that the relative contents of NAA and Cho in these two sites were lower than those in the normal control group [39]. However, the study of Boucard et al. showed that there was no significant difference in the content of NAA and Cho in patients with glaucoma [40]. The discrepancies between these studies, apart from methodology and inclusion criteria, might also reflect differences in the metabolism of visual centers in different stages of glaucoma.

7.1.2.4 BOLD-fMRI

The working principle of BOLD-fMRI is the blood oxygen level dependence (BOLD) effect: when the neuron is excited, its electrical activity causes a significant increase in local cerebral blood flow, and also increases the consumption of oxygen; thus the combined effect is the increased local blood oxygen content and the decreased deoxygenated hemoglobin content. Due to the different properties of oxygen, hemoglobin, and deoxyhemoglobin in the magnetic field, the final expression is the enhancement of T2-weighted image signal in stimulated areas of brain. fMRI uses a fast scanning MRI sequence, which has good spatial and temporal resolution, and can directly reflect the areas and characteristics of neural functional changes under different stimulations [41]. Observation of clinical glaucoma patients with fMRI found that BOLD in primary visual cortex of glaucoma patients decreased consistently with visual field deficits [42]. Further studies by Wang Ningli et al. discovered that visual cortical responses to visual stimuli were decreased in the residual central visual field of glaucoma patients, suggesting that the damage of visual cortical neurons in glaucoma is not only consistent with the visual field defect, but also might be earlier than the visual field defects [42, 43].

7.1.2.5 Arterial Spin Labeling (ASL)

ASL uses radio-frequency pulse to achieve magnetic reversal of hydrogen protons in the water molecules of the arterial blood flowing to the brain near the plane of the brain, to finish magnetic labeling of arterial blood and to use it as an endogenous contrast agent. Blood perfusion of the whole brain or various specific regions under resting and functional conditions could be quantitatively measured without the injection of contrast agents. Thus ASL is superior to other current blood flow imaging methods in both temporal and spatial resolution [44]. The researchers found that differences in the blood flow between the ventral and dorsal cortices of the primary visual cortex were significantly associated with differences in the upper and lower visual fields with ASL techniques, suggesting that the resting blood perfusion of visual cortex is consistent with the extent of visual field damage in glaucoma patients. The changes of cerebral blood flow may be involved in glaucomatous optic nerve injury and may be a marker of retinal posterior visual pathway injury [45].

7.1.2.6 Transcranial Doppler (TCD)

In addition to ASL, another simple, noninvasive, sensitive method of reflecting blood flow in brain is TCD. Harris et al. discovered that the mean and systolic peak blood flow velocities of middle cerebral artery (MCA) in glaucoma patients were significantly lower than those of normal subjects by TCD, and the average flow rate of MCA was related to the amplitude, contrast sensitivity, visual field defect degree, and

LogMAR visual acuity of patients' ERG. At the same time, the MCA of glaucoma patients showed no response to hyperoxia, which is different from the fact that the mean and systolic peak flow velocity of MCA in normal individuals exhibit significant decrease when breathing hyperoxia [46, 47]. These results suggest that glaucoma patients have regulatory and reactive abnormalities in the cerebral vessels that dominate the optic pathway, and these reactive abnormalities may also result in visual impairment in glaucoma patients. Professor Wang Ningli et al. used TCD technology to observe the vascular reactivity of the posterior cerebral artery (PCA), the main vascularization of visual cortex of occipital lobe in glaucoma patients. The results showed that the blood flow resistance of bilateral PCA in patients with glaucoma was significantly higher than that of the normal control group. After visual stimulation was given in normal residual central visual field of glaucoma patients, the increase range of bilateral PCA blood flow was significantly lower than that in normal control group. Meanwhile, the decrease range for blood flow of bilateral PCA was significantly lower in patients with glaucoma than in the control group when the blood resistance was increased by the deep and rapid respiratory stimulation of 2HZ [48]. The findings firstly discovered anomalies in hemodynamics and vascular reactivity of the posterior segment of the optic pathway in glaucoma patients, which might be secondary to changes of neurons and glial cells in posterior visual pathway, as well as local manifestations in patients with declined systemic vascular autoregulation function. Because of the noninvasive nature of the TCD scan, the hemodynamic changes of PCA were earlier than those of glaucomatous visual field defects. Therefore, it may be used as a sensitive indicator of visual center damage in glaucoma patients for clinical application. Abnormal cerebral perfusion provides new ideas and directions for the study on visual central change of optic nerve injury, i.e., glaucoma, and it is of great significance.

7.2 Conclusion

In summary, neuroimaging technologies may prove useful in assessing the spread of glaucomatous damage within the central nervous system. It is possible for us to observe the changes of structure, metabolism, neuronal activity, and blood perfusion of optic center in glaucoma patients with modern neuroimaging technique in a simple, noninvasive, sensitive, and accurate way. These results not only provide a basis for our further understanding of glaucoma, but also provide new ideas and methods for researches on other eye diseases and neural system diseases, which is of great significance for the development of new clinical treatment.

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82:844–51.
2. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004;363:1711–20.
3. Nicolela MT. Clinical clues of vascular dysregulation and its association with glaucoma. Can J Ophthalmol. 2008;43:337–41.
4. Grieshaber MC, Mozaffarieh M, Flammer J. What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol. 2007;52(Suppl. 2):S144–54.
5. Emre M, Orgul S, Gugleta K, Flammer J. Ocular blood flow alteration in glaucoma is related to systemic vascular dysregulation. Br J Ophthalmol. 2004;88:662–6.
6. Tezel G, Wax MB. The immune system and glaucoma. Curr Opin Ophthalmol. 2004;15:80–4.
7. Schwartz M, London A. Erratum to: immune maintenance in glaucoma: boosting the body's own neuroprotective potential. J Ocul Biol Dis Infor. 2009;2:104–8.
8. Schori H, Kipnis J, Yoles E, et al. Vaccination for protection of retinal ganglion cells against death from glutamate cytotoxicity and ocular hypertension: implications for glaucoma. Proc Natl Acad Sci U S A. 2001;98:3398–403.
9. Yucel Y, Gupta N. Glaucoma of the brain: a disease model for the study of transsynaptic neural degeneration. Prog Brain Res. 2008;173:465–78.
10. Yucel YH, Gupta N, Zhang Q, et al. Memantine protects neurons from shrinkage in the lateral geniculate nucleus in experimental glaucoma. Arch Ophthalmol. 2006;124:217–25.
11. Yucel YH, Zhang Q, Gupta N, et al. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. Arch Ophthalmol. 2000;118:378–84.
12. Yucel YH, Zhang Q, Weinreb RN, et al. Atrophy of relay neurons in magno-and parvocellular layers in the lateral geniculate nucleus in experimental glaucoma. Invest Ophthalmol Vis Sci. 2001;42:3216–22.
13. Yucel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. Prog Retin Eye Res. 2003;22:465–81.
14. Gang S, Jinghua W, Jing X, et al. Impairment on neurons of lateral geniculate nucleus in rats with chronic ocular hypertension. Recent Adv Ophthalmol. 2005;6:522–4.
15. Sasaoka M, Nakamura K, Shimazawa M, et al. Changes in visual fields and lateral geniculate nucleus in monkey laser-induced high intraocular pressure model. Exp Eye Res. 2008;86:770–82.
16. Wang X, Sam-Wah TS, Ng YK. Nitric oxide, microglial activities and neuronal cell death in the lateral geniculate nucleus of glaucomatous rats. Brain Res. 2000;878:136–47.
17. Zhang S, Wang H, Lu Q, et al. Detection of early neuron degeneration and accompanying glial responses in the visual pathway in a rat model of acute intraocular hypertension. Brain Res. 2009;1303:131–43.
18. Crawford ML, Harwerth RS, Smith EL 3rd, et al. Experimental glaucoma in primates: changes in cytochrome oxidase blobs in V1 cortex. Invest Ophthalmol Vis Sci. 2001;42:358–64.
19. Crawford ML, Harwerth RS, Smith EL 3rd, et al. Glaucoma in primates: cytochrome oxidase reactivity in parvo-and magnocellular pathways. Invest Ophthalmol Vis Sci. 2000;41:1791–802.
20. Vickers JC, Hof PR, Schumer RA, et al. Magnocellular and parvocellular visual pathways are both affected in a macaque monkey model of glaucoma. Aust N Z J Ophthalmol. 1997;25:239–43.

21. Chan KC, So KF, Wu EX. Proton magnetic resonance spectroscopy revealed choline reduction in the visual cortex in an experimental model of chronic glaucoma. Exp Eye Res. 2009;88:65–70.
22. Lam DY, Kaufman PL, Gabelt BT, To EC, Matsubara JA. Neurochemical correlates of cortical plasticity after unilateral elevated intraocular pressure in a primate model of glaucoma. Invest Ophthalmol Vis Sci. 2003;44:2573–81.
23. Gupta N, Ang LC, Noel de Tilly L, et al. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. Br J Ophthalmol. 2006;90:674–8.
24. Nucci C, Martucci A, Cesareo M, et al. Brain involvement in glaucoma: advanced neuroimaging for understanding and monitoring a new target for therapy. Curr Opin Pharmacol. 2013;13:128–33.
25. Dai H, Mu KT, Qi JP, et al. Assessment of lateral geniculate nucleus atrophy with 3T MR imaging and correlation with clinical stage of glaucoma. AJNR Am J Neuroradiol. 2011;32:1347–53.
26. Hernowo AT, Boucard CC, Jansonius NM, et al. Automated morphometry of the visual pathway in primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2011;52:2758–66.
27. Boucard CC, Hernowo AT, Maguire RP, et al. Changes in cortical grey matter density associated with long-standing retinal visual field defects. Brain. 2009;132:1898–906.
28. Chen WW, Wang N, Cai S, et al. Structural brain abnormalities in patients with primary open-angle glaucoma: a study with 3T MR imaging. Invest Ophthalmol Vis Sci. 2013;54:545–54.
29. Li C, Cai P, Shi L, et al. Voxel-based morphometry of the visual-related cortex in primary open angle glaucoma. Curr Eye Res. 2012;37:794–802.
30. Garaci FG, Bolacchi F, Cerulli A, et al. Optic nerve and optic radiation neurodegeneration in patients with glaucoma: in vivo analysis with 3-T diffusion-tensor MR imaging. Radiology. 2009;252:496–501.
31. Chen Z, Lin F, Wang J, et al. Diffusion tensor magnetic resonance imaging reveals visual pathway damage that correlates with clinical severity in glaucoma. Clin Exp Ophthalmol. 2013;41:43–9.
32. El-Rafei A, Engelhorn T, Wärntges S, et al. Glaucoma classification based on visual pathway analysis using diffusion tensor imaging. Magn Reson Imaging. 2013;31(7):1081–91.
33. Chang ST, Xu J, Trinkaus K, et al. Optic nerve diffusion tensor imaging parameters and their correlation with optic disc topography and disease severity in adult glaucoma patients and controls. J Glaucoma. 2013;23(8):513–20.
34. Murai H, Suzuki Y, Kiyosawa M, et al. Positive correlation between the degree of visual field defect and optic radiation damage in glaucoma patients. Jpn J Ophthalmol. 2013;57:257–62.
35. Dai H, Yin D, Hu C, et al. Whole-brain voxel-based analysis of diffusion tensor MRI parameters in patients with primary open angle glaucoma and correlation with clinical glaucoma stage. Neuroradiology. 2013;55:233–43.
36. Boucard CC, Mostert JP, Cornelissen FW, et al. Visual stimulation, 1H MR spectroscopy and fMRI of the human visual pathways. Eur Radiol. 2005;15:47–52.
37. Block W, Traber F, Flacke S, et al. In-vivo proton MR-spectroscopy of the human brain: assessment of N-acetylaspartate (NAA) reduction as a marker for neurodegeneration. Amino Acids. 2002;23:317–23.
38. Gomez-Anson B, Alegret M, Munoz E, et al. Decreased frontal choline and neuropsychological performance in preclinical Huntington disease. Neurology. 2007;68:906–10.
39. Zhang Y, Chen X, Wen G, et al. Proton magnetic resonance spectroscopy ((1) H-MRS) reveals geniculocalcarine and striate area degeneration in primary glaucoma. PLoS One. 2013;8(8):e73197.
40. Boucard CC, Hoogduin JM, van der Grond J, Cornelissen FW. Occipital proton magnetic resonance spectroscopy (1H-MRS) reveals normal metabolite concentrations in retinal visual field defects. PLoS One. 2007;2:222.
41. Ogawa S, Lee TM, Kay AR, et al. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A. 1990;87:9868–72.
42. Duncan RO, Sample PA, Weinreb RN, et al. Retinotopic organization of primary visual cortex in glaucoma: comparing fMRI measurements of cortical function with visual field loss. Prog Retin Eye Res. 2007;26:38–56.
43. Qing G, Zhang S, Wang B, et al. Functional MRI signal changes in primary visual cortex corresponding to the central normal visual field of patients with primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2010;51:4627–34.
44. Floyd TF, Ratcliffe SJ, Wang J, Resch B, Detre JA. Precision of the CASL-perfusion MRI technique for the measurement of cerebral blood flow in whole brain and vascular territories. J Magn Reson Imaging. 2003;18:649–55.
45. Duncan RO, Sample PA, Bowd C, et al. Arterial spin labeling fMRI measurements of decreased blood flow in primary visual cortex correlates with decreased visual function in human glaucoma. Vis Res. 2012;60:51–60.
46. Harris A, Siesky B, Zarfati D, et al. Relationship of cerebral blood flow and central visual function in primary open-angle glaucoma. J Glaucoma. 2007;16:159–63.
47. Harris A, Zarfati D, Zalish M, et al. Reduced cerebrovascular blood flow velocities and vasoreactivity in open-angle glaucoma. Am J Ophthalmol. 2003;135:144–7.
48. Zhang S, Xie Y, Yang J, et al. Reduced cerebrovascular reactivity in posterior cerebral arteries in patients with primary open-angle glaucoma. Ophthalmology. 2013;120:2501–7.

Part III

Life Activities and Eye Diseases

Circadian Rhythm and the Physiology and Pathology of Eye

8

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8.1 Introduction

With the proposing and popularizing of the concept of " holistic integrative medicine," people have moved their perspective from an isolated organ to the entire human body, and from the view of whole body further explore the relationship between human body and local organs at the level of internal body and analyze the interaction between the environment and the body at the level of external body, with the purpose of finding out the inner and close relationship from some of the past seemingly irrelevant things. "Circadian rhythm" is somehow strange for most ophthalmologists and far away from our usual study. But actually, "circadian rhythm" is the strongest rhythm system inside organisms, which can adjust the physiological rhythm and behavior according to the cycle of sun exposure. Light change is an important stimulus signal to the regulation of rhythm of the central. Eyes, which receive the light of outside world, without doubt, will have a complex relationship with circadian rhythm. In this section, we describe the basic concepts of biological rhythms, discuss the material basis and regulatory mechanisms of circadian rhythms with the most relevant to vision, and also introduce the interaction effect between circadian rhythm and physiology and pathology of the eye. It is expected that readers can understand the link between biological rhythm and ophthalmology after reading this chapter, and then deeply integrate the knowledge system related to biological rhythm and eye diseases by applying the concept of holistic integrative medicine, to better optimize the diagnosis and treatment of eye diseases.

8.1.1 Overview of Biological Rhythm (Biorhythm)

In the earth, from blue algae to human beings, all organisms' life activities are cyclical, and there exists a certain rule. This rhythmic life activity is called biorhythm. Biorhythm is one of the basic characteristics of life activities. It is gradually formed in the process of biological evolution, in order to adapt to changes in the environment [1–4].

According to different rhythm cycles, biological rhythm can be divided into the following categories:

8.1.1.1 Circadian Rhythm

The cycle of circadian rhythm is 20–28 h. It is the strongest biological rhythm of the body. Since sun exposure is the most important factor of environmental change, almost all living beings can adjust their physiological rhythms and behavior according to the cycle of sun exposure [4–6]. For humans, many physiological and behavioral rhythms, including sleep-wake cycle, body temperature, and hormone levels, are characterized by circadian rhythms.

8.1.1.2 Ultradian Rhythm

The cycle of ultradian rhythm is less than 20 h. The common ultradian rhythm in human beings includes heartbeat and breathing movement, the cycle of which is about 1 and 3 s, respectively. Marine life usually has circasemidian rhythm due to the impact of tidal cycle, with the cycle of about 12 h, which is near to the tidal cycle of 12.4 h.

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_8

8.1.1.3 Infradian Rhythm

The cycle of infradian rhythm is longer than 28 h. The common rhythms are as follows:

1. Circasemiseptan rhythm: The rhythm cycle is 70–98 h, around 3.5 days. The cosmic ray, solar electromagnetic field, and earth's magnetic field all have this rhythm change. Moreover, this rhythm is also present in human blood pressure, heart rate, and other physiological activities.
2. Circaseptan rhythm: Circaseptan rhythm is a common biorhythm in infradian rhythms, with the cycle of 140–196 h, about 7 days. This rhythm is present in the life activities of animals, such as activity level, body temperature, and blood pressure and other changes.
3. Circamensual rhythm: The cycle of circamensual rhythm is 25–35 days (about a month). Women's menstrual activity is the most typical representative of circamensual rhythm. In addition, this rhythm is also present in endocrine, blood pressure, and metabolic activity of the body.
4. Circannual rhythm: The cycle of circannual rhythm is about 305–425 days. The rooting, germination, flowering, and fruiting of plants repeating in a cycle period of 1 year and migratory bird's migrating behaviors from winter to spring both are the typical representatives of circannual rhythm. Life activities of human bodies also have changes in circannual rhythm.

8.1.2 Material Basis and Regulation of Circadian Rhythm

Circadian rhythm is the most basic biorhythm. Earth rotation is the most important factor that causes the change of natural environment in the earth. The rotation causes light changes between day and night (including ultraviolet light) and temperature variation, which make all living beings generate the circadian rhythm during their evolutions, thus adjusting their internal life activities based on outside environment changes.

The external factors that can influence circadian rhythm are called zeitgeber. For mammals, the light, food, and drugs can also be used as zeitgeber to influence and regulate circadian rhythm, while the light is the most important one. In case of no zeitgeber guiding, the rhythm of mammal itself (i.e., free-running rhythm) will not be consistent with the 24-h cycle of earth's light and dark, but exists with some deviation. Only under the guiding of external light signal or other zeitgeber rhythm self-adjust system of living beings can make their circadian rhythm keep pace with outside environment. Light is the most important zeitgeber. This process is called the light guiding effect of circadian rhythm. Light guiding effect also allows internal clock to be adjusted according to the time zone during travel and the length of day and night in different seasons. It is very necessary that internal biological clock can be adjusted synchronously according to changes in external environment for maintaining a good physiological and psychological condition. If the internal biological clock cannot be adjusted in time, jet leg or other discomfort could happen [3].

In mammals, circadian rhythms are widespread in cell, tissue, and organ layers. From general perspective, the regulation system of circadian rhythm is also present, consisting of multiple inner connected parts such as retina, suprachiasmatic nucleus, and pineal gland. Retina can feel the change of light. Suprachiasmatic nucleus is the system center of circadian rhythm which plays a major role in the generation, maintenance, and regulation of circadian rhythm. Pineal gland is the target organ for suprachiasmatic nucleus signal outputs. The melatonin produced by pineal gland can act on the surrounding tissue and adjust circadian rhythm. Melatonin can also feed back the effect to suprachiasmatic nucleus itself. After the external light perceived by the retina, the signal generated by the retina will be passed to suprachiasmatic nucleus through retinal hypothalamus beam, guiding circadian rhythm, and then causing the phase movement of circadian rhythm. This process helps internal circadian rhythm of body keep pace with the diurnal cycle of external environment [1, 4].

8.1.3 Relationship Between Eye Physiology and Sleep Regulation

The regulation of circadian rhythm depends on light changing, while the light changing is received by eyes and further influences nerve regulation central. Therefore, besides visual function, eyes also have the capability of circadian rhythm regulation, pupillary light reflex, and other nonimage-forming visual functions.

The studies in recent years have found that there is a kind of retinal ganglion cells with endogenous photoreceptor in mammal's retina. In this kind of cells, melanopsin is used as photopigment. Melanopsin is a new opsin-like molecule with the characteristics of retinal vision pigment. It contains retinal chromophore, and like all G protein-coupled receptors melanopsin has a seven-band transmembrane structure with a lysine residue in the seventh transmembrane structure. This is a specific structure for opsin where retinal chromophore attaches. These melanopsin-containing retinal ganglion cells have direct photoreactivity, with the ability to convert electromagnetic radiation into transmembrane potentials. That's why these cells are also known as retinal ganglion cells with endogenous photoreceptors. The absorption spectra peak of these cells is 480 nm. Unlike the

rod-and-cone photoreceptors, these endogenous photosensitive retinal ganglion cells have a sustained photoreaction under light, and this kind of photoreaction can last for hours even without exogenous chromophore supply [5–7].

This kind of retinal ganglion cells with endogenous photoreceptors express melanopsin. They are morphologically similar to the third class of retinal ganglion cells, with smaller cell bodies (16–20 μm), 2–3 less branched long dendrites, usually extending to 300 μm. Dendritic ends are distributed at the OFF and ON subshell of inner molecular layer. The retinal ganglion cells in rat's retina account for about 2.5% of all retinal ganglion cells, and that is 1% in the retina of mice [8]. The studies of Gooley and Morin et al. [9, 10] have shown that the melanopsin-containing retinal ganglion cells project not only to the suprachiasmatic nucleus directly to involve in the regulation of circadian rhythms, but also to the brain regions including intergeniculate leaflet and olivary pretectal nuclei which relate with circadian rhythm regulation, pupil light reflex, and hypogastric region surrounding the ventricle as well as the ventrolateral region of preoptic nucleus. These regions are all involved in sleep and rhythm regulation.

Although the melanopsin-containing retinal ganglion cells and the cone-rod system are involved in nonimage-forming visual function, their functions are not exactly same. Lucas et al. [11] did a study on melanopsin-knockout mice about their pupillary light reflex. When bright monochromatic light is used to stimulate mouse pupil, wild-type mice pupil contracts faster and becomes smaller than melanopsin-knockout mice pupil. There is no significant difference in the speed and size of pupil contraction between wild-type mice and melanopsin-knockout mice when they were stimulated with dimmer light. The previous research of Lucas [12] has found that the sensitivity of the pupillary light reflex is significantly decreased for the mice (rd/rd, cl) which lost cone-rod cell degeneration. However, there is no significant difference in pupil contraction with wild-type mice pupil under bright-light stimulation. These experimental results indicate that the melanopsin-containing retinal ganglion cells and cone-rod cells are complementary with each other in the process of mediating the pupillary light reflex. Pupillary light reflex relies mainly on the melanopsin-containing retinal ganglion cells in bright-light environment, and mainly on cone-rod cells to mediate in dimmer-light environment. In order to quantitatively measure the complementary relationship between them, Lucas et al. measured the pupillary light reflex for melanopsin-knockout mice, cone-rod cell degeneration mice, and wild-type mice under the same light stimulation, and draw the trend curve of pupil contractions for three kinds of mice under three different light intensity stimulations, and then through summing the pupil contraction results of melanopsin-knockout mice and cone-rod cell degeneration mice according to corresponding formulas calculated the expectation result of pupil contraction degree. The results have showed that the expected value is completely consistent with the actual value of pupil contraction in wild-type mice. This indicates that there is no other photoreceptor in addition to the melanopsin-containing retinal ganglion cells and cone-rod cells.

Hatter et al. [13] produced melanopsin and rod-cone three-gene knockout mice by destroying melanopsin, cone-and-rod genes. As a result, the intrinsic light reactions of the melanopsin-containing retinal ganglion cells and the light conduction of the traditional rod-cone photoreceptors are destroyed. These mice completely lost pupillary light reflex, incapable of producing physiological rhythm according to the light and dark cycle. Pandan et al. [14] knocked out the melanin protein gene of the mice with rd mutant and got the same result. The physiological rhythm and masking reaction of the mice disappeared.

It is proved that the endogenous photosensitive retinal ganglion cell system and the traditional rod-cone system are the light perception system of the eye, which plays an important role in the circadian rhythm, pupillary light reflex and other nonimage-forming visual functions. No other systems are involved in nonimage-forming visual functions.

Melanopsin-containing retinal ganglion cell pathway and cone-rod cell pathway are complementary not only in function, but also in anatomical structures. Morphological studies have found that about one-fourth of the melanopsin-containing ganglion cells, bipolar cells, and amacrine cells do have direct synaptic links [15]. The results of electrophysiological studies also show that there are α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA) and γ-aminobutyric acid (GABA) type A receptor on part of melanopsin-containing retinal ganglion cells [16]. The latest findings have suggested that the cone-rod cell pathway and the melanopsin-containing retinal ganglion cell pathway are functionally integrated on the melanopsin-containing retinal ganglion cells, to further involve in the regulation of nonimage-forming visual function [17]. In the primate mammalian, melanopsin-containing ganglion cells are not only associated with bipolar cells and amacrine cells from an anatomical perspective, but their photographic properties are also easily affected by the rod-cone cells. Short-wavelength cone cell signaling weakens its photoreaction, whereas signal arriving from rod cells and medium- and long-wavelength cone cells can enhance its photoreaction [18].

So far, the nonimage-forming visual pathway of mammal has been clarified. When external light passes through the eye refractive system and reaches the retina, the optical signal, directly via the melanopsin-containing retina ganglion cells or by the way of being conducted to melanopsin-containing retina ganglion cells through the rod-cone cells,

can be transmitted to the suprachiasmatic nucleus, ventral lateral geniculate nucleus, intergeniculate leaflet, and olivary pretectal nucleus and other visual centers, to complete the generation and regulation of circadian rhythm, pupillary light reflex, and other nonimage-forming visual functions.

8.1.4 The Impact of Eye Pathology on Circadian Rhythm

Therefore, it is easy to imagine that the eye diseases, which may damage the melanopsin-containing retinal ganglion cells, the rod-cone cells, will not only destroy the image-forming visual function, but also affect the patients' signal transduction in nonimage-forming visual pathway. This will lead to dysfunction of circadian rhythm (can be expressed as sleep disorder), pupillary light reflex abnormalities, and so on.

The lack of zeitgeber can lead to circadian rhythm disorders, usually causing sleep disorders. Circadian rhythm disorders, defined as mismatches between sleep-wake cycle and circadian time in the environment, can be caused by exposure reduction to light-dark cycles (the most important zeitgeber for circadian rhythm) or reduction of optical signal transmission resulted by ocular diseases (such as the elderly type of small pupil, cataract, diabetic retinopathy, age-related macular degeneration, retinitis pigmentosa, and glaucoma) [19, 20]. The related research has indicated that in contrast to normal people, the sleep quality of retinitis pigmentosa (RP) patients in the same age group was worse, and the degree of visual impairment was proportional to the degree of sleep loss [21]. These abnormalities are caused by the lack of optical signals that transmit the circadian clock and are related to the degree of loss of photoreceptors.

In humans, it has been reported that the patients with varying degrees of blindness caused by a variety of eye diseases will have sleep disorders and abnormal circadian rhythm. Because of the loss of light-guiding action, endogenous circadian rhythm cannot be synchronized with the external light-dark cycle. This makes partial-blind patients have the independent rhythm (free-running) which is asynchronous with 24 h in external environment or irregular circadian rhythm and other performance. By detecting the rhythms of melatonin secretion in blind patients, some studies have shown that some blind patients still have normal circadian rhythms and are synchronized with the 24-h light-dark cycle in external environment; some do not show significant circadian rhythms, and the remaining patients become free-running. Later studies have demonstrated that changes in circadian rhythm are directly related to the degree of patient's light sensitivity. In a study of 49 blind patients, 19 patients had partial photoreception, and the other 30 patients had no photoreception. Among the 19 patients with partial photoreception, 14 (74%) patients kept a normal circadian rhythm and the decrease in visual acuity in the light-sensitive group did not affect the occurrence of circadian rhythm abnormality. Among the 30 patients without photoreception, 23 (77%) patients had no normal circadian rhythm, and 17 (74%) of them showed free-running, especially for those with unilateral and bilateral eyeball extracted [20, 21]. These patients who lost normal circadian rhythms showed a series of sleep disorders, including cyclical insomnia, delayed sleep latency, reduced sleep time, increased sleep awakening, and daytime sleepiness. And the patient with the lowest level of photoreception showed the most severe sleep disorder.

As a typical optic nerve degeneration disease, distinctive damage of glaucoma is the chromic progressive degeneration and loss of retinal ganglion cells and axons. They will lead to nerve fiber layer defects, optic nerve atrophy, and other pathological changes, which are clinically manifested by the visual function decline, and distinctive fundus optic disk changes and visual field defects. So, will glaucoma cause damage to such retinal ganglion cells and affect the biological rhythm?

Retinal ganglion cells can be classified as superior collicular retinal ganglion cells (scRGCs) and melanopsin-containing retinal ganglion cells (mcRGCs). Many previous studies have focused on scRGCs, and found that intraocular pressure elevation can cause loss of scRGCs. Previous clinical studies have shown that glaucoma patients exhibit relative afferent pupillary defect (RAPD) in the early stages of the disease, and the tendencies of sleep disorders in the late stage [19, 22]. Foreign studies have found that the probability of occurrence of insomnia, snoring which is manifested by obstructive sleep apnea syndrome (OSA) [23, 24] in severe cases, excessive daytime sleepiness, and other issues in glaucoma patients is significantly higher than that in the normal control group. Some clinical studies in China have also found that the proportion of primary glaucoma patients with sleep disorders was significantly higher than the proportion of normal control group [25]. Does the above study suggest that glaucoma does cause a change in the biological rhythm? How is its mechanism? Because the mechanism of biological rhythm regulation is still not clear, it is hard to make a detailed analysis of this result.

With the discovery of melanopsin-containing retinal ganglion cells, new progress has been made. Animal experiments have confirmed that acute high intraocular pressure can cause pathological changes of mcRGC in mice, showing as decreased cell density and dendritic branch reduction; the axoplasmic transport of suprachiasmatic nucleus projected by mcRGC slowed down and reduced. The degree of damage is similar with scRGCs. Chronic ocular hypertension can

cause the density of mcRGCs in rats to decrease, and the severity of mcRGC reduction is similar to that of scRGCs. The above studies suggest that high intraocular pressure causes damage on the image-forming visual system and nonimage-forming visual system, and the degree of damage is similar [26, 27]. Drouyer et al. [28] found that experimental glaucoma caused an overall reduction (about 60%) in the projection fibers of the mouse retina to the brain, which was particularly severe in the suprachiasmatic nucleus, by up to about 71%. For dorsal lateral geniculate nucleus, intergeniculate leaflet, and olivary pretectal nucleus, it reduced by about 60–65%. For ventral lateral geniculate nucleus, superior colliculus, it is reduced by about 50%. Moreover, chronic intraocular pressure elevation caused changes of mouse runner rhythm.

However, some animal studies also found that in the chronic ocular hypertension model, there was a significant loss of scRGCs in the experimental eye. The difference was statistically significant ($P < 0.001$), and consistent with previous studies. But there was no significant loss of mRGCs after 12 weeks of induction of chronic ocular hypertension ($P > 0.05$), and no pathological changes were observed for any dendritic form [29].

Although most animal experiments support that high intraocular pressure will damage the nonimage-forming visual system and affect the biological rhythm, does this phenomenon also happen clinically? Pittsburgh Sleep Quality Index (PSQI) is a common subjective evaluation method of sleep quality, with good reliability and repeatability. Through the analysis of PSQI sleep quality among 99 patients with primary open-angle glaucoma, 52 patients with primary angle-closure glaucoma, and 199 normal subjects, it is observed that the proportion of sleep disorder in patients with primary open-angle glaucoma and primary angle-closure glaucoma was significantly higher than that in the normal population. Within the two groups of patients there was no significant difference in the proportion of sleep disorders. The proportion of sleep disorders is positively correlated with the severity of visual field damage. For open-angle glaucoma patients, 24-h intraocular pressure measurements were performed. Based on the time at which the intraocular pressure peak appeared, the patients were divided into two groups, the nocturnal group and diurnal group. And the proportion of sleep disorders between the two groups had no significant difference, indicating that the patient sleep disorder is not caused by increased intraocular pressure at night. The above study suggests that patients with primary glaucoma may have a sleep-wake cycle disorder due to the fact that the melanopsin-containing retinal ganglion cells are injured, which damages the nonimage-forming visual pathway, resulting in a biological rhythm disorder [30].

8.2 Summary

Biological rhythm is one of the basic characteristics of life activities. It has an important impact on biological behavior. With deep research on the basic area of retinal nerve loops, the clinical understanding and treatment of retinal diseases will inevitably be improved. The relationship between retinal disease and biological rhythm becomes increasingly clear. The above study indicates that due to eye diseases which prevents light from entering the eyes effectively, regulation of biological rhythm will be affected. And some diseases with photoreceptor damage will cause light-guiding action to weaken or even disappear because the light can't be accepted into the eyes effectively. Basic and clinical trials have shown that there is an abnormal regulation of biological rhythm for glaucoma patients. Therefore, in clinical work, for patients with eye diseases that could affect the nonimage-forming visual pathways, the attention should be given not only to their visual function damages, but also to their circadian rhythm disorders and other symptoms. It is also appropriate to do clinical intervention for cases with serious injury.

References

1. Halberg F. Chronobiology:a science in tune with the rhythms of life. Minneapolis, MN: Bolger; 1986. p. 9–10.
2. Breaus T, Cornelissen G, Halberg F, et al. Temporal associations of life with solar and geophysical activity. Ann Geophys. 1995;13:1211–22.
3. Smolensky MH. Introduction to chronobiology. New York: Springer; 1983. p. 1–12.
4. Wang Z. Chronobiology. Beijing: Beijing Science; 2006.
5. Lucas RJ, Douglas RH, Foster RG. Characterization of an ocular photopigment capable of driving pupillary constriction in mice. Nat Neurosci. 2001;4(6):621–6.
6. Provencio I, Jiang G, De Grip WJ, Hayes WP, Rollag MD. Melanopsin: an opsin in melanophores, brain, and eye. Proc Natl Acad Sci U S A. 1998;95:340–5.
7. Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MD. A novel human opsin in the inner retina. J Neurosci. 2000;20:600–5.
8. Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science. 2002;295:1065–70.
9. Gooley JJ, Lu J, Fischer D, Saper CB. A broad role for melanopsin in nonvisual photoreception. J Neurosci. 2003;23:7093–106.
10. Morin LP, Blanchard JH, Provencio I. Retinal ganglion cell projections to the hamster suprachiasmatic nucleus, intergeniculate leaflet, and visual midbrain: bifurcation and melanopsin immunoreactivity. J Comp Neurol. 2003;465(3):401–16.
11. Lucas RJ, Hattar S, Takao M, Berson DM, Foster RG, Yau KW. Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice. Science. 2003;299:245–7.

12. Lucas RJ, Freedman MS, Munoz M, Garcia-Fernandez JM, Foster RG. Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. Science. 1999;284:505–7.
13. Hattar S, Lucas RJ, Mrosovsky N, et al. Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. Nature. 2003;424:76–81.
14. Panda S, Provencio I, Tu DC, et al. Melanopsin is required for non-image-forming photic responses in blind mice. Science. 2003;301:525–7.
15. Belenky MA, Smeraski CA, Provencio I, Sollars PJ, Pickard GE. Melanopsin retinal ganglion cells receive bipolar and amacrine cell synapses. J Comp Neurol. 2003;460:380–93.
16. Perez-Leon JA, Warren EJ, Allen CN, Robinson DW, Brown RL. Synaptic inputs to retinal ganglion cells that set the circadian clock. EurJ Neurosci. 2006;24:1117–23.
17. Hatori M, Le H, Vollmers C, et al. Inducible ablation of melanopsin-expressing retinal ganglion cells reveals their central role in non-image forming visual responses. PLoS One. 2008;3:e2451.
18. Dacey DM, Liao HW, Peterson BB, et al. Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature. 2005;433:749–54.
19. Waller EA, Bendel RE, Kaplan J. Sleep disorder and the eye. Mayo Clin Proc. 2008;83(11):1251–61.
20. Lockley SW, Skene DJ, Arendt J, et al. Relationship between melatonin rhythms and visual loss in the blind. J Clin Endocrinol Metab. 1997;82(11):3763–70.
21. Gordo MA, Recio J, Sanchez-Barcelo EJ. Decreased sleep quality in patients suffering from retinitis pigmentosa. J Sleep Res. 2001;10(2):159–64.
22. Jean-Louis G, Zizi F, Lazzaro DR, et al. Circadian rhythm dysfunction in glaucoma: a hypothesis. J Circ Rhythm. 2008;6:1.
23. McNab AA. The eye and sleep apnea. Sleep Med Rev. 2007; 11(4):269–76.
24. Sergi M, Salerno DE, Rizzi M, et al. Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients. J Glaucoma. 2007;16:42–6.
25. Yang J, Lin Z. Investigation of sleep disturbance in patients with primary glaucoma. Chin J Misdiagnostics. 2007;7:2168–9.
26. Wang HZ, Lu QJ, Wang NL, et al. Loss of melanopsin-containing retinal ganglion cells in a rat glaucoma model. Chin Med J. 2008;121(11):1015–9.
27. Wang H, Hong J, Wang N. Effect of acute ocular hypertension on retinal ganglion cells containing melanopsin in rats. Chin Ophthalmic Res. 2009;27(7):558–62.
28. Drouyer E, Dkhissi-Benyahya O, Chiquet C, et al. Glaucoma alters the circadian timing system. PLoS One. 2008;3(12):e3931.
29. Li RS. Melanopsin-expressing retinal ganglion cells are more injury-resistant in a chronic ocular hypertension model. Invest Ophthalmol Vis Sci. 2006;47(7):2951–8.
30. Wang H, Zhang Y, Ding J, et al. Changes in the circadian rhythm in patients with primary glaucoma. PLoS One. 2013;8(4):e62841.

9 The Relationship Between the Physiology and Pathology and the Intraocular Pressure

Jie Hao, Ningli Wang, and Hui Juan Wu

9.1 Introduction

Intraocular pressure is the pressure that eyeball contents act on the eyeball wall, and is essential for maintaining eyeball shape and physiological function. Like blood pressure, intraocular pressure keeps a dynamic balance state. Its stability depends on the dynamic balance between formation rate of aqueous humor, aqueous humor discharge rate, and episcleral venous pressure. Any factors causing this balance change will affect the changes in intraocular pressure. In the past, people are accustomed to study eyeball as an independent organ rather than part of the entire body, and even often ignore the effect of episcleral venous pressure. However, from the concept of holistic integrative medicine perspective and the overall view, the whole cycle of the body, its activities, and interaction with the surrounding environment are closely related with the organs. The physiological state of the body, such as gender, blood pressure, and breathing; the lifestyle, such as diet, exercise, and body position; and the pathological state, such as diabetes, high blood pressure, and hemodialysis, will all have an impact on intraocular pressure. And changes in intraocular pressure will conversely affect the systemic physiological and pathological conditions. It is expected that from this chapter, readers can re-examine the intraocular pressure from the overall view and fully consider all aspects of the body factors when analyzing intraocular pressure levels and changes.

Intraocular pressure (referred to as "IOP") is the pressure that eyeball contents act on the wall of eyeball, with physiological reference range as 15.27 ± 2.57 mmHg (10 ~ 21 mmHg), which is right-biased non-normal Gaussian distribution. The stability of intraocular pressure depends on the dynamic balance between aqueous humor formation rate, aqueous humor discharge rate, and episcleral venous pressure. Any factors that cause this balance change will affect the changes in intraocular pressure.

IOP is closely related to systemic physiological factors, including intrinsic physiological characteristics and external physiological activities. In physiological case, intraocular pressure has a certain range of circadian fluctuations. However, the significant increase or decrease of intraocular pressure associates with the imbalance of physiological status, and to a certain extent it reflects the corresponding systemic pathological changes. This section explains the relationship between intraocular pressure and systemic physiology and pathology as bellows:

9.1.1 The Relationship Between Intraocular Pressure and Systemic Physiology

9.1.1.1 Physiological Characteristics

Age

Intraocular pressure changes with age. In general, intraocular pressure increases with increasing age. The intraocular pressure of adults is higher than that of infants and young children. Between 20 and 40 years old, intraocular pressure follows Gaussian distribution, and increases with increasing age. However, studies have suggested that intraocular pressure decreases with increasing age [1]. In a cohort study from Singapore, it has showed that before the age of 60, intraocular pressure increases with age, and after the

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_9

age of 60, with age increasing the intraocular pressure decreases instead [2]. Mansouri et al. [3] compared the circadian fluctuation range and peak of intraocular pressure in normal elderly (53–71 years) and normal young people (18–25 years), and found that between these two age groups there was no significant difference in the fluctuation range of intraocular pressure. But the peak in elderly group was significantly delayed compared with that of young group. The causes of association between intraocular pressure and age are speculated to be the fact that the generation and outflow of aqueous humor are associated with the changes of age.

Gender

Previous studies have reported that the intraocular pressure of women is higher than that of men [4], while this conclusion is not confirmed in some studies. In a study of 7313 subjects who underwent intraocular pressure measurements, there was no statistically significant difference between the genders [5]. Women's menstrual cycle does not cause changes in intraocular pressure, but during ovulation or gestational the intraocular pressure could be slightly lower. For postmenopausal women, the average intraocular pressure is higher than the men in same age.

The Ocular Axial and Refractive Status

Regardless of the postural changes, previous studies [6, 7] have confirmed that there is correlation between intraocular pressure, ocular axial, and refractive status. A large number of studies have shown that myopia (long axial) patients could have higher intraocular pressure. Also, increased intraocular pressure can also cause the increase of axial length.

In the case of taking postural changes into account, for the IOP fluctuation, the difference of intraocular pressure between supine position and sitting position in hyperopia group (short axial length) is greater than that of the myopia group (long axial length), which means that the shorter the axial length, the bigger the intraocular pressure fluctuations caused by postural changes, and the more severe the myopia, the smaller the intraocular pressure fluctuations. So with shorter axial length, postural changes will cause more intraocular pressure fluctuations. The reason of abovementioned [8] was speculated to be the fact that a shorter axial length leads to greater redistribution of choroidal blood flow.

Blood Pressure

There was a correlation between blood pressure and systemic blood pressure. Studies have shown that by increasing 100 mmHg blood pressure, intraocular pressure increases 2 mmHg [9]. In general, the changes in each arterial pressure cycle can cause intraocular pressure fluctuations from 1 to 3 mmHg [10].

There was a positive correlation between episcleral venous pressure and intraocular pressure. A study showed that the degree of elevation or decrease between them was in a parallel state.

Respiratory Movements

Respiratory exercise can cause transient changes in perfusion pressure, which further leads to transient changes in intraocular pressure. When exhalation resistance increases, uvea congestion will also increase, so will the intraocular pressure. For example the intraocular pressure of wind instrument players can increase from 24 to 46 mmHg in a short period of 12 s [11]. Therefore, long-term, frequent breath-hold action (Valsalva) is a risk factor for glaucoma-specific visual field damage.

Hormone Secretion

The fluctuation of intraocular pressure may be related to the circadian changes of hormone secretion. Glucocorticoids, adrenocorticotropic hormone, corticotropin-releasing hormone, and growth hormone can cause increased intraocular pressure, while progesterone, estrogen, and chorionic gonadotropin can cause decreased intraocular pressure [12].

Neuromodulation

A large number of studies have shown that intraocular pressure is regulated by the nervous system. In general, sympathetic nerve excitement can cause intraocular pressure to transiently decline, and aqueous humor filtration rate to increase; adrenergic receptor agonists and cyclic adenosine monophosphate reduce intraocular pressure through this mechanism.

Intraocular pressure can also be regulated by parasympathetic nerve. Stimulating the oculomotor nerve can decrease intraocular pressure; pterygopalatine ganglion is another dominant parasympathetic ganglion, so intraocular pressure may also be decreased through blocking pterygopalatine ganglion of glaucoma patients [13].

The central nervous system has a regulatory effect on intraocular pressure. Stimulating many parts of the brain, such as stimulating the posterior ventral region of hypothalamus and dorsal hypothalamus, can cause changes of intraocular pressure.

Circadian Rhythm

In normal people, the circadian fluctuation of intraocular pressure ranged from 3 to 6 mmHg if the measurement postural remained unchanged, while the circadian fluctuation of glaucoma patients was more obvious. Previous studies suggested that the circadian fluctuation of intraocular pressure followed a repeatable pattern in most people, which was that the peak of intraocular pressure was in the morning and the

valley value appeared in the afternoon or at night. In 1990, David [14] reviewed 690 curves of intraocular pressure measured by the Goldmann applanation tonometer in sitting position, and found that the average fluctuation of intraocular pressure in normal eyes (84 cases) was 5.0 ± 2.7 mmHg, and was 5.8 ± 2.9 mmHg in open-angle glaucoma eyes (140 cases) and 6.8 ± 3.2 mmHg in ocular hypertension eyes (350 cases). The study also showed that in 40% of the curves, intraocular pressure peak appeared in the morning, and in 65% of the curves, peak appeared before noon. However, in some people, the intraocular pressure peak appeared at night. Except for the circadian postural changes, the circadian fluctuation of intraocular pressure may be due to circadian fluctuations in aqueous humor production. But recent studies have suggested that this factor may not be the main reason for circadian fluctuations in intraocular pressure, because the production of aqueous humor decreases at night and increases during the day, which is not consistent with the phenomenon that some of the pressure peak appears at night. Another study suggests that the circadian changes in intraocular pressure fluctuate with cyclical changes in hormone levels; in particular, the intraocular pressure peak appears more regularly after 3–4 h of plasma cortisol release.

9.1.1.2 Physiological Activity

Postural Changes

Physiological postural changes can cause intraocular pressure changing. Compared with the normal people, the fluctuations of intraocular pressure caused by postural changes in glaucoma patients are more obvious, especially for glaucoma patients who have normal intraocular pressure [15]. Through reviewing the previous studies, in glaucoma patients, the elevation of intraocular pressure caused by postural changes ranged from 3.9 to 9.3 mmHg [15–17], and in normal people the range was 2.9 to 8.6 mmHg [6, 15–18]. The mechanisms by which postural changes cause increased intraocular pressure are more pronounced as choroidal congestion and episcleral venous pressure increase [19]. Kiuchi et al. [20] consider that the visual field progression of glaucoma patients with normal intraocular pressure is related with the range of intraocular pressure elevation caused by postural changes. It is conjectured that supine sleep will accelerate the progression of such patients. Jain et al. [21] required the subjects to use 12.7 cm height pillow, which can make patients' head lift up to about 15° to relieve intraocular pressure increasing caused by supine position. Buys et al. [22] let glaucoma patients raise head up to 30° to a horizontal position at night, and compared with the supine position intraocular pressure was decreased by 3.2 mmHg with a 20% drop. Baskaran et al. [23] found that the change of intraocular pressure in the inverted position was twice that of the sitting position. Recently, some scholars paid their attention to the changes in intraocular pressure in lateral position. Lee et al. [24] analyzed the intraocular pressure in normal people with lateral position for 5 and 30 min. It was found that for eyes in the position of lower side, the intraocular pressure was significantly higher compared with supine position. After keeping the same position for 30 min, and restoring to supine position, the intraocular pressure was significantly decreased.

Exercise

As early as in 1963, some scholars found that intraocular pressure can be reduced by exercise. After aerobic exercise, intraocular pressure of glaucoma patients might be decreased by an average of 4.6 mmHg. Firstly, according to different modes, the exercise was divided into isotonic exercise and isometric exercise, and the former included walking, jogging, and running. In normal subjects, the intraocular pressure drop was 2.43 ± 0.30 mmHg, 3.85± 0.55 mmHg, and 4.00 ± 0.37 mmHg [25], respectively, after this mode of exercise, and in glaucoma patients the reduction of intraocular pressure was more compared with normal people. Isometric exercise refers to the exercise in which the muscle contracts and muscle fibers do not shorten, such as lifting weights and maintaining a certain posture. Will the isometric exercise decrease the intraocular pressure or not? There is no unified conclusion. Dickerman et al. [26] found that in athletes the intraocular pressure increased from 13 + 2.8 mmHg to 28.0 + 9.3 mmHg before and after weight lifting. Secondly, according to different exercise intensity [27], when the exercise intensity was up to 70%, 55%, and 40% of the maximum, the decline degree of intraocular pressure in normal subjects decreased. Moreover, according to different exercise time, long-term exercise is better than short-term movement in reducing intraocular pressure [28].

Dietary Intake

Intake of caffeinated foods, drinking, smoking, etc. may affect the intraocular pressure. Drinking may reduce intraocular pressure. Studies showed that the incidence of ocular hypertension was lower in drinkers than that in nondrinkers, suggesting that drinking may inhibit the release of antidiuretic hormone, which might reduce the interstitial fluid entering into the eye, and directly inhibit the production of aqueous humor.

Drinking lots of water may increase the intraocular pressure, and water drinking test is used as a method to detect the peak of intraocular pressure in glaucoma patients.

9.1.2 The Relationship Between Intraocular Pressure and Systemic Pathology

9.1.2.1 High Blood Pressure

Epidemiological studies showed that there was a positive correlation between hypertension and intraocular pressure.

In Blue Mountains Eye Study [29], it was reported that when systolic blood pressure changed from less than 110 mmHg to higher than 200 mmHg, the intraocular pressure increased by 3.4 mmHg; meanwhile when diastolic blood pressure changed from less than 70 mmHg to higher than 120 mmHg, intraocular pressure also increased by 3.4 mmHg.

9.1.2.2 Diabetes

Epidemiological studies showed that there was a positive correlation between diabetes and intraocular pressure. In a Singapore Malay Eye Disease Study [30], 3280 subjects with the age of 40 to 80 years were examined, and the result showed that the incidence of diabetes was associated with a slight increase in intraocular pressure.

9.1.2.3 Obesity

Studies showed that obesity is associated with increase of intraocular pressure. Possible mechanisms included excessive accumulation of adipose tissue in the orbit which may increase episcleral venous pressure and affect the drainage of the aqueous humor; and obesity may induce endothelial dysfunction and self-regulation imbalance, especially significant in diabetic patients. In addition, increase of intraocular pressure may be related to obesity-induced systemic diseases such as hypertension and diabetes.

9.1.2.4 Inflammation

Body's inflammatory response may result in decrease of intraocular pressure, which may be related to less production of aqueous humor when inflammation occurs. However, if the effect of inflammation on the drainage pathway injury of aqueous humor is greater compared to the production pathway blocking of aqueous humor, it may have potential risk of an increase in intraocular pressure.

9.1.2.5 Others

In addition to the above factors, other pathological conditions associated with intraocular pressure include high fever, obstructive sleep apnea syndrome, hemoglobin agglutination, and acromegaly, all of which may cause the increase of intraocular pressure, and myotonic dystrophy, acquired human immunodeficiency syndrome (human immunodeficiency virus, HIV), which may cause the decrease of intraocular pressure.

9.2 Summary

The intraocular pressure is closely related to the changes in systemic physiological characteristics and physiological status, involving multiple systems of the body. Under the adjustment of variable regulatory mechanisms, intraocular pressure keeps a dynamic balance state. Any factor that affects the dynamic balance can cause changes in intraocular pressure, which may be closely related to systemic pathological changes. Attention should be paid to the relationship between intraocular pressure and systemic physiology and pathology, which may provide evidence for the diagnosis of relevant diseases, and important information for understanding the disease as a whole.

References

1. Shiose Y. The aging effect on intraocular pressure in an apparently normal population. Arch Ophthalmol. 1984;102(6):883–7.
2. Wong TT, Wong TY, Foster PJ, et al. The relationship of intraocular pressure with age, systolic blood pressure, and central corneal thickness in an Asian population. Invest Ophthalmol Vis Sci. 2009;50(9):4097–102.
3. Mansouri K, Weinreb RN, Liu JH. Effects of aging on 24-hour intraocular pressure measurements in sitting and supine body positions. Invest Ophthalmol Vis Sci. 2012;53(1):112–6.
4. Leske MC, Connell AM, Wu SY, et al. Distribution of intraocular pressure. The Barbados Eye Study. Arch Ophthalmol. 1997; 115(8):1051–7.
5. Fukuoka S, Aihara M, Iwase A, et al. Intraocular pressure in an ophthalmologically normal Japanese population. Acta Ophthalmol. 2008;86(4):434–9.
6. Liu JH, Kripke DF, Hoffman RE, et al. Nocturnal elevation of intraocular pressure in young adults. Invest Ophthalmol Vis Sci. 1998;39(13):2707–12.
7. Loewen NA, Liu JH, Weinreb RN. Increased 24-hour variation of human intraocular pressure with short axial length. Invest Ophthalmol Vis Sci. 2010;51(2):933–7.
8. Malihi M, Sit AJ. Effect of head and body position on intraocular pressure. Ophthalmology. 2012;119(5):987–91.
9. Bulpitt CJ, Hodes C, Everitt MG. Intraocular pressure and systemic blood pressure in the elderly. Br J Ophthalmol. 1975;59(12):717–20.
10. Langham ME, To'Mey KF. A clinical procedure for the measurements of the ocular pulse-pressure relationship and the ophthalmic arterial pressure. Exp Eye Res. 1978;27(1):17–25.
11. Schuman JS, Massicotte EC, Connolly S, et al. Increased intraocular pressure and visual field defects in high resistance wind instrument players. Ophthalmology. 2000;107(1):127–33.
12. Wang N, Ye T. Clinical glaucoma atlas. Beijing: People's Medical Publishing House; 2007.
13. Li M. Glaucoma. Beijing: People's Medical Publishing House; 2004.
14. David R, Zangwill L, Briscoe D, et al. Diurnal intraocular pressure variations: an analysis of 690 diurnal curves. Br J Ophthalmol. 1992;76(5):280–3.
15. Tsukahara S, Sasaki T. Postural change of IOP in normal persons and in patients with primary wide open-angle glaucoma and low-tension glaucoma. Br J Ophthalmol. 1984;68(6):389–92.
16. Fogagnolo P, Orzalesi N, Ferreras A, et al. The circadian curve of intraocular pressure: can we estimate its characteristics during office hours? Invest Ophthalmol Vis Sci. 2009;50(5):2209–15.
17. Krieglstein G, Langham ME. Influence of body position on the intraocular pressure of normal and glaucomatous eyes. Ophthalmologica. 1975;171(2):132–45.
18. Liu JH, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. Invest Ophthalmol Vis Sci. 1999;40(12):2912–7.
19. Prata TS, Kanadani FN. Eye pressure and head position. Ophthalmology. 2010;117(11):2236–7.

20. Kiuchi T, Motoyama Y, Oshika T. Relationship of progression of visual field damage to postural changes in intraocular pressure in patients with normal-tension glaucoma. Ophthalmology. 2006;113(12):2150–5.
21. Jain MR, Marmion VJ. Rapid pneumatic and Mackey-Marg applanation tonometry to evaluate the postural effect on intraocular pressure. Br J Ophthalmol. 1976;60(10):687–93.
22. Buys YM, Alasbali T, Jin YP, et al. Effect of sleeping in a head-up position on intraocular pressure in patients with glaucoma. Ophthalmology. 2010;117(7):1348–51.
23. Baskaran M, Raman K, Ramani KK, et al. Intraocular pressure changes and ocular biometry during Sirsasana (headstand posture) in yoga practitioners. Ophthalmology. 2006;113(8): 1327–32.
24. Lee JY, Yoo C, Jung JH, et al. The effect of lateral decubitus position on intraocular pressure in healthy young subjects. Acta Ophthalmol. 2012;90(1):e68–72.
25. Qureshi IA. Effects of mild, moderate and severe exercise on intraocular pressure of sedentary subjects. Ann Hum Biol. 1995; 22(6):545–53.
26. Dickerman RD, Smith GH, Langham-Roof L, et al. Intra-ocular pressure changes during maximal isometric contraction: does this reflect intra-cranial pressure or retinal venous pressure? Neurol Res. 1999;21(3):243–6.
27. Kiuchi Y, Mishima HK, Hotehama Y, et al. Exercise intensity determines the magnitude of IOP decrease after running. Jpn J Ophthalmol. 1994;38(2):191–5.
28. Liang Y, Wu Y, Li S, et al. Exercise and intraocular pressure. Chin J Ophthalmol. 2011;47(9):4.
29. Mitchell P, Lee AJ, Wang JJ, et al. Intraocular pressure over the clinical range of blood pressure: blue mountains eye study findings. Am J Ophthalmol. 2005;140(1):131–2.
30. Tan GS, Wong TY, Fong CW, et al. Diabetes, metabolic abnormalities, and glaucoma. Arch Ophthalmol. 2009;127(10):1354–61.

Psychological Abnormality and Glaucoma

10

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10.1 Introduction

As a part of the "integrated" human body, the eye will inevitably be affected by the "integrated" environment. In this "integrated" environment, in addition to the most commonly mentioned physiological conditions such as blood pressure, breathing and hormones, the psychological environment also affects the local condition of eyes and the occurrence of the disease, which is the idea of "integrative ophthalmology." Glaucoma is an ancient disease, which is only initially regarded as an independent ocular disease. The research related to glaucoma is also limited to the local anatomy and the changes of pathological and physiological function. As early as the nineteenth century, people have realized that glaucoma has certain relevance with psychological factors. With the development of psychological research methods, the study of the correlation between glaucoma and psychological factors is deepened accordingly. How does the psychological factor affect the onset and progression of glaucoma? How do these two situations affect each other? At least in the traditional anatomy and physiology, these two situations have nothing to do with each other. This is exactly what we should consider from the perspective of integrated medicine. In this section, the psychological personality and emotional characteristics of glaucoma patients are summarized, and the commonly used assessment methods are introduced. Moreover, the relationship between disease development and psychological characteristics is explained. After reading this section, it is expected that readers can realize that the adjustment of the patient's mood can be used as one of the adjuvant treatment methods of glaucoma. In the future, the psychological state of patients may be consciously taken into account in the diagnosis and treatment of glaucoma.

As early as the nineteenth century, people have realized that glaucoma has certain relevance with psychological factors. Researchers have found that emotional incentives can cause acute attack of the glaucoma with increased intraocular pressure in some glaucoma patients [1–3]. With further studies, Ripley et al. [3, 4] found that mood fluctuation might not only lead to acute attack of glaucoma (rapid increase in intraocular pressure), but also affect the fluctuation of intraocular pressure in daily life, and furthermore they pointed out that emotional instability, overanxiety, and hypochondria tended to be the general psychological characteristics of glaucoma patients. Since then, people began to perform psychological assessment for glaucoma patients, and compared the results with other patients' [5, 6]. However, there are some shortcomings in the early studies on the personality of glaucoma patients, such as the small sample value, lack of statistical significance, and more importantly larger difference in diagnostic classification of glaucoma [7]. Chronic simple glaucoma and acute congestive glaucoma were changed to open-angle glaucoma and angle-closure glaucoma, and more attention to optic nerve injury was paid in glaucoma diagnosis [8].

The recent psychological assessment of glaucoma patients is mainly performed in open-angle glaucoma patients [1, 7, 9–13]. The conclusion of these studies was that open-angle glaucoma patients had the feature of mood swing prone (neuroticism) compared with normal people or patients with other eye diseases. Based on these studies, it was hypothesized that patients with angle-closure glaucoma have the same emotional characteristics as open-angle glaucoma patients, especially for those with acute attack of glaucoma who may be more susceptible to fluctuations in mood. But currently there is still relatively a lack of the study for angle-closure glaucoma. In China, a large proportion of patients were with angle-closure glaucoma. A study was conducted in order to comprehensively understand the psychological characteristics of the glaucoma population and the effects of disease status and other related factors on the psychological

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https://doi.org/10.1007/978-981-13-7896-6_10

status of the glaucoma patient. The study included patients with primary angle closure (PAC), primary angle-closure glaucoma (PACG), and primary open-angle glaucoma (POAG). The main purpose of the study was to compare the differences in the psychological characteristics between PACG patients and POAG patients, and to explore the related factors that affected the psychological state of patients.

Psychological state assessment indicators can be divided into two types of psychological variables. One is the personality trait of patients, which is relatively stable, reflecting the individual's consciousness, emotion, and behavioral predispositions [14]. The Eysenck Personality Questionnaire (EPQ) is used to assess the personality traits of patients. The other one is the emotional characteristics of patients, including transience and mutability [14]. In this survey, we have mainly assessed the anxiety and depression of the patients, using the Zung Self-Rating Depression Scale (SDS) and the Zung Self-Rating Anxiety Scale (SAS).

The Eysenck Personality Questionnaire is a personality assessment scale based on Eysenck's personality theory. The verification of Chinese version and the production of norm are taken charge by professor Gong Yaoxian [15]. The Chinese version of the questionnaire contains 88 questions with the assessment of a total of personality traits in four dimensions: E on behalf of the introversion and extroversion, N on behalf of the neuroticism, P on behalf of the psychoticism, and L on behalf of the lie. The production of norm is based on the results of the questionnaire detection for 6418 subjects (2517 adults and 3901 children). The original score of the survey is converted to T points and then evaluated. The conversion is based on the gender of the subjects and the mean and standard deviation of the population at certain age. The average of T points is 50 and the standard deviation is 10.

The Zung Self-Rating Depression Scale is a self-rating scale with 20 entries, and the results of the assessment show depressive symptoms of the patient. According to the episode frequency of symptoms, the score of each entry is ranged from 1 to 4, and the higher score means more frequent attack. Although the score of the scale cannot be used as a standard for clinical diagnosis of depression, it can show the severity of depressive symptoms. The assessment of total score is divided into four levels: "less than 40 points" represents normal or no obvious pathological symptoms; "40 to 47 points" represents mild depression; "48 to 55 points" represents moderate depression; and "56 points or more" represents severe depression [16]. The verification of Chinese version and the production of norm are based on a survey of 1340 people [17]. The average of this scale in China is 33.46 with the standard deviation of 8.55.

The Zung Self-Rating Anxiety Scale is a self-rating scale with 20 entries that detects the patient's anxiety symptoms. The structure of the questionnaire is the same as that of SDS. The Chinese version of the questionnaire is translated from English and has been verified, with a normal score of 20 to 40 [18].

The medical history, ophthalmologic examination, and psychological status of patients with different types of glaucoma were summarized in the study. It showed that the scores of EPQ neuroticism in the glaucoma patient group (POAG group and PACG group) were significantly higher than those in the non-glaucoma patient group (PAC group and cataract control group). There were no significant differences between the groups in terms of self-rating anxiety score (SAS), self-rating depression score (SDS), and other three scores of EPQ (introversion and extroversion, psychoticism, and lie). Neuroticism is one of the four personality traits based on Eysenck's theory of personality. The high score suggests that the patient has emotional problems that are prone to mood fluctuation and are prone to neuroticism. Symptoms of neuroticism mainly include anxiety, panic, depression, phobia, hypochondria, paranoia, and hysteria [19, 20]. Lim et al. [9] found that compared with the control group, open-angle glaucoma patients had some psychological characteristics such as hypochondriasis and hysteria and were more concerned about health problems. According to Lim's study, psychological problems of glaucoma patients were mainly related to health status.

The form of the disease has a certain impact on the psychological state of patients. Based on our findings, acute attack of glaucoma reduced the neuroticism of glaucoma patients; that is, the psychological state of glaucoma patients who experience acute episodes is more stable than that of glaucoma patients without acute episodes. What is the reason for this result? In the study of other diseases, it had been reported [21, 22] that the neuroticism and hypochondriasis score was significantly lower than before in the patients who were cured or whose symptoms had been obviously relieved, while the patients with the symptoms unrelieved might maintain the psychological characteristics of neuroticism [21]. For glaucoma patients, acute attack of increased intraocular pressure is a very dramatic process. The symptoms include severe eye pain, nausea and vomiting, headache, blurred vision, or halos vision. These symptoms would disappear after proper treatment. Although sometimes the treatment was not enough leading to glaucomatous optic nerve damage, the patients still felt that they were cured because they no longer suffered from the aforementioned symptoms. For chronic glaucoma patients, in the initial stage of the disease they had no symptoms, and after treatment the patient did not feel any improvement or even felt worse because of glaucoma surgery [23, 24] or long-term usage of eye drops [25]. The reasons above may explain why the acute attack of

the PACG group has a lower neuroticism score compared to the chronic PACG and POAG groups.

The data in this study also have showed that the N-score of glaucoma patients is associated with how long the patients had been diagnosed of glaucoma. The longer the patients have glaucoma, the higher the N-score is. The years of diagnosis is positively correlated with not only the N-score but also the SAS score (correlation coefficient = 0.325, $p = 0.007$), but it has no correlation with the SDS score (correlation coefficient = 0.027, $p = 0.829$). There is no similar report so far according to our survey data. This may perhaps be due to the fact that in different studies, different psychometric tools and evaluation criteria were used, and the subjects were also different in these studies. The current study was a cross-sectional research, so it was not possible to determine that the higher level of nervousness and anxiety was related to the time of diagnosis or the long-term adherence to hospital. Because the subjects were the glaucoma patients in the hospital, and moreover people's psychological state would affect their behavioral characteristics, the result could not be applied to nonhospital patients. For more objective study, it is necessary to conduct a population survey and to follow up the psychological changes of patients before and after diagnosis.

Based on this survey, we found that the mood of glaucoma patients (PACG and POAG) was more easily fluctuated compared with non-glaucoma patients (PAC and cataract control group); the mode of onset (whether it is an acute attack or not) had an impact on the patients' emotional stability. As the patients' emotional fluctuation may affect the intraocular pressure through nervous system [4], the emotional regulation of patients can be used as one of the alternative treatment of glaucoma. Understanding the related factors that affect the psychological state of glaucoma patients can make it easier in the psychological adjustment of the patient.

References

1. Pache M, Flammer J. A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma. Surv Ophthalmol. 2006;51:179–211.
2. Schoenberg MJ. Psychosomatic relationships and their therapeutic implications in glaucoma. Trans Am Ophthalmol Soc. 1939;37:134–49.
3. Ripley H, Wolff HG. Life situations, emotions, and glaucoma. Life situations, emotions, and glaucoma. Psychosom Med. 1950;12:215–24.
4. Erb C, Thiel HJ, Flammer J. The psychology of the glaucoma patient. Curr Opin Ophthalmol. 1998;9:65–70.
5. Berger AS, Zimet CN. Personality features of patients with primary glaucoma: a medico psychosocial exploration. Psychosom Med. 1959;21:389–96.
6. Zimet CN, Berger AS. Emotional factors in primary glaucoma: an evaluation of psychological test data. Psychosom Med. 1959;22:391–9.
7. Mabuchi F, Yoshimura K, Kashiwagi K, et al. Personality assessment based on the five-factor model of personality structure in patients with primary open-angle glaucoma. Jpn J Ophthalmol. 2005;49:31–5.
8. Foster PJ, Buhrmann R, Quigley HA, et al. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86:238–42.
9. Lim MC, Shiba DR, Clark IJ, et al. Personality type of the glaucoma patient. J Glaucoma. 2007;16:649–54.
10. Erb C, Batra A, Lietz A, et al. Psychological characteristics of patients with normal-tension glaucoma. Graefe's Arch Clin Exp Ophthalmol. 1999;237:753–7.
11. Jampel HD, Frick KD, Janz NK, et al. Depression and mood indicators in newly diagnosed glaucoma patients. Am J Ophthalmol. 2007;144:238–44.
12. Wilson MR, Coleman AL, Yu F, et al. Depression in patients with glaucoma as measured by self-report surveys. Ophthalmology. 2002;109:1018–22.
13. Pappa C, Hyphantis T, Pappa S, et al. Psychiatric manifestations and personality traits associated with compliance with glaucoma treatment. J Psychosom Res. 2006;61:609–17.
14. Scheier MF, Bridges MW. Person variables and health: personality predispositions and acute psychological states as shared determinants for disease. Psychosom Med. 1995;57:255–68.
15. Gong Y. Eysenck personality questionnaire manual. Changsha: Hunan Map Publishing House; 1992.
16. Wang X, Wang X, Ma H. ZUNG self-rating depression Scale. Manual of mental health assessment scale (updated version). Beijing: China Journal of Mental Health; 1999. p. 194–7.
17. Wang C. The depression self – rating scale was used to evaluate 1340 normal people. Chin J Nerv Ment Dis. 1986;12(5):267–8.
18. Wu W. Self-rating anxiety scale (SAS). Shanghai Arch Psych, 1990, 2 updated version: 44.
19. Tyrer P, Alexander J, Remington M, et al. Relationship between neurotic symptoms and neurotic diagnosis: a longitudinal study. J Affect Disord. 1987;13:13–21.
20. Chinese psychiatric Association: classification and diagnostic criteria of mental disorders in China-third-edition (CCMD-3). Chinese Psychiatric Association, 2001.
21. Jess P, Bech P. The validity of Eysenck's neuroticism dimension within the Minnesota multiphasic personality inventory in patients with duodenal ulcer. The Hvidovre ulcer project group. Psychother Psychosom. 1994;62:168–75.
22. Barnes D, Gatchel RJ, Mayer TG, et al. Changes in MMPI profile levels of chronic low back pain patients following successful treatment. J Spinal Disord. 1990;3:353–5.
23. Feiner L, Piltz-Seymour JR. Collaborative initial Glaucoma treatment study: a summary of results to date. Curr Opin Ophthalmol. 2003;14:106–11.
24. Baudouin C. Side effects of antiglaucomatous drugs on the ocular surface. Curr Opin Ophthalmol. 1996;7:80–6.
25. Denis P, Nordmann JP, Elena PP, et al. central nervous system control of intraocular pressure. Fundam Clin Pharmacol. 1994;8:230–7.

Exercise and Physiology and Pathology of the Eye

11

Yingxin Yang, Ningli Wang, and Hui Juan Wu

11.1 Introduction

"Life exists in exercise"; "Life is more than exercise"; "A rolling stone gathers no moss." Since ancient times, both Chinese and foreign scholars have been aware of and stressed the importance of exercise to human life. Exercise is important; however, are all exercises suitable for each individual? Can the same exercise produce similar effects in all individuals? This is actually the research idea of "holistic integrative medicine"—integrating the research for diseases or local organs into the whole body and the broader environment. At the same time, when studying the disease or local organ function in the same environment and interference factors, individual personality cannot be ignored. "The human body needs exercise, but it should not be excessive. Moderate exercise can help the food digested and absorbed, make the blood circulation well, and prevent disease." This conclusion shows that in ancient China, people have explored the relationship between the exercise and human health with the integrative thinking of the human body and the environment. As the vital organ of the body, how is "eye" affected by the exercise? In this section, the following topics will be discussed: the effects of exercise on intraocular pressure and its mechanism, the effects of exercise on eye-related serum factors, the effects of exercise on eye blood flow, and the probable damage of the eye caused by exercise. It is expected that after reading this chapter, readers can get revelation, and then understand the relationship between exercise and physiology and pathology of the eye from a new perspective and from the integrated point of view, considering the adjustment of exercise as one of the effect factors when diagnosing and treating patients.

Exercise has been reported to reduce the risk of the occurrence and development of many systemic diseases, such as diabetes, hypertension, and other cardiovascular diseases [1]. The effect of exercise on the eye is mainly related to the intraocular pressure, ocular blood flow, and serum factor. In the diseases of the eye, the relation between glaucoma and exercise is closest.

11.1.1 Exercise and Intraocular Pressure

Some scholars have noted that in daily life, intraocular pressure is closely related to people's diet, behavior, and other lifestyle [2]. It was firstly reported by Janiszewska-Zygier [3] in 1963 that exercise may make the intraocular pressure decreased, and later a large numbers of studies were reported. In the recent half century, the research on exercise and intraocular pressure has clearly confirmed that rapid exercise including dynamic exercise and isometric exercise can rapidly reduce intraocular pressure [4]. After aerobic exercise [5], intraocular pressure can be reduced by 1–8 mmHg in normal people; after jumping exercise [6], the intraocular pressure is decreased by 5.07 ± 1.76 mmHg, and after climbing the mountain intraocular pressure is decreased by 9.5–15.5 mmHg.

11.1.1.1 The Effect of Exercise on Intraocular Pressure in Glaucoma Patient

Primary open-angle glaucoma had relationship with systemic cardiovascular disease, hypotension, anemia, or immune abnormalities [7]. As early as 1965, Cooper et al. [8] conducted a study of exercise and glaucoma, and it had been

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https://doi.org/10.1007/978-981-13-7896-6_11

reported that the intraocular pressure was decreased after exercise, and which was more severe in glaucoma patients [9]. In glaucoma patients, the intraocular pressure was reduced by 12.86 ± 2.05 mmHg after exercise, and the amplitude of intraocular pressure decreasing is closely related to exercise intensity [6].

In primary open-angle glaucoma patients, after low-intensity exercise (20% maximal exercise for 10 min) and high-intensity exercise (60% maximal exercise for 5 min), the intraocular pressures of right eye were 16.60 ± 4.15 mmHg and 13.71 ± 3.73 mmHg, respectively, and it was significantly reduced compared with 19.40 ± 4.23 mmHg before exercise. The intraocular pressures of left eye were 16.74 ± 4.83 mmHg and 13.58 ± 4.64 mmHg, respectively, and it was also significantly reduced compared with 19.13 ± 4.08 mmHg before exercise.

In open-angle glaucoma patients using anti-glaucoma medications, the maximum intraocular pressure drop after exercise was up to 56% with an average of 5.72 ± 3.34 mmHg.

After exercise, intraocular pressure changed with time in a certain pattern: the lowest intraocular pressure was achieved immediately after exercise, then in the following 1 h the pressure increased quickly, and 2 h later the intraocular pressure kept a stable state, as shown in Fig. 11.1.

In about 52% of the glaucoma patients, the intraocular pressure returned to the pre-exercise level 1 h after exercise, and the average time of recovery was 1.5 h. In about 26% of the patients, the pressure returned to pre-exercise level 2 h later, and 7% of patients were recovered in 0.5 h, or 3 h and 4 h later, as shown in Fig. 11.2.

11.1.1.2 Refractive Status and Intraocular Pressure Reduction After Exercise

Epidemiological studies have shown that refractive status was closely related to glaucomatous optic nerve damage, especially in high myopia [10–12]. The open-angle glaucoma patients with high myopia showed the characteristics including higher average intraocular pressure [13], smaller circadian fluctuation of intraocular pressure, and significantly higher intraocular pressure fluctuation than that of non-high-myopia eyes [14], while the high-myopia eyes had the characteristics of lower average intraocular pressure, and greater circadian fluctuations of intraocular pressure [15].

In open-angle glaucoma patients with high myopia (myopia of −6.00D or more), after 10 min of low-intensity (20% W_{max}) exercise, intraocular pressure was reduced by 3.41 ± 2.77 mmHg, which was significantly greater than that of open-angle glaucoma patients with non-high myopia (myopia lower than −6.00D, but more than −0.75D) (1.51 ± 2.98 mmHg) and that of open-angle glaucoma patients with non-myopia (myopia lower than −0.75D, and hypermetropia lower than +0.75D) (3.17 ± 3.02 mmHg).

In open-angle glaucoma patients with high myopia, the intraocular pressure was decreased by 7.45 ± 3.47 mmHg after 5 min of high-intensity (60% W_{max}) exercise, which was significantly greater than that of open-angle glaucoma patients with non-high myopia (4.78 ± 2.58 mmHg) and open-angle glaucoma patients with non-myopia (4.75 ± 3.38 mmHg).

Moreover, in three groups of open-angle glaucoma patients with different refractive states, the reduction range of intraocular pressure after high-intensity exercise was significantly higher compared with that after low-intensity exercise (Fig. 11.3).

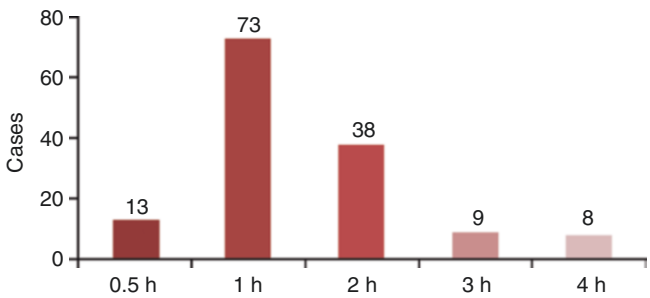

Fig. 11.2 The distribution of the subjects in different time periods of the intraocular pressure recovery time after exercise. Cases: 0.5 small, 0.5, 1, 2, 3, 4

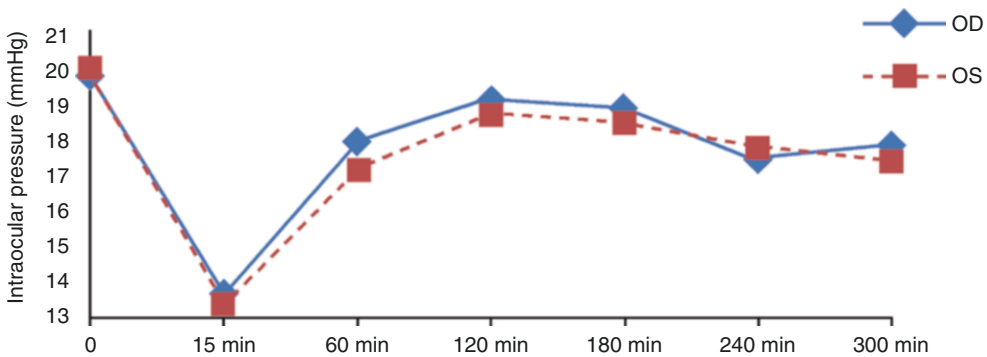

Fig. 11.1 Recovery of IOP over time after binocular movement. Intraocular pressure 15 min, 60 min. 120 min, 180 min, 240 min, 300 min

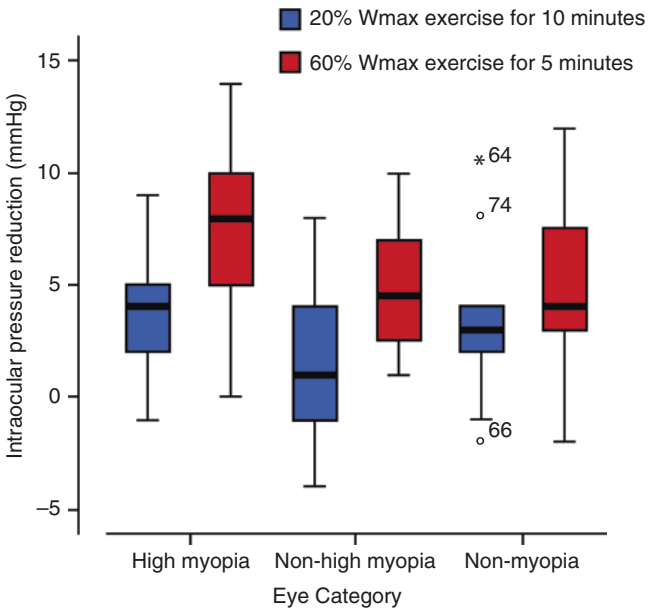

Fig. 11.3 Distribution of IOP reduction after exercise of different intensities in open-angle glaucoma patients. Intraocular pressure reduction, High myopia, Non-high myopia, Non-myopia, Eye category, 20% W_{max} exercise for 10 min. 60% W_{max} motion, 60% W_{max} exercise for 5 min

11.1.1.3 The Impact of Long-Term Exercise on Intraocular Pressure

It is generally believed that after long-term exercise, the physical condition may be improved, and baseline intraocular pressure will be reduced in glaucoma patients. Furthermore, the intraocular pressure fluctuations after exercise can be decreased [16]. Senol reported that [17] after 3 months of aerobic exercise, the intraocular pressure can be reduced by 20%, and the intraocular pressure was back to pre-exercise level in 3 weeks after discontinuing exercise. After 3 months of aerobic exercise, the intraocular pressure of right eye was 18.44 ± 3.91 mmHg at 8 o'clock, which was significantly lower than that of glaucoma patients with no exercise (20.49 ± 4.83 mmHg). The left eye showed the same characteristics as those in the patients with exercise, the intraocular pressure was 19.16 ± 3.55 mmHg, and in the patients with no exercise the pressure was 19.67 ± 4.83 mmHg. This decreased tendency of intraocular pressure may be related to the habit of morning exercise in most people. The average of intraocular pressure in 24 h also presented the decreased tendency. After 3 months of aerobic exercise, the average intraocular pressure of glaucoma patients was 19.19 ± 2.89 mmHg in the right eye and 19.26 ± 3.15 mmHg in the left eye. For the patients without exercise, the intraocular pressure was 19.26 ± 3.15 mmHg in the right eye and 19.80 ± 4.12 mmHg in the left eye.

11.1.1.4 The Impact of Exercise on Intraocular Pressure Fluctuations

It is controversial that whether the intraocular pressure fluctuation is an independent risk factor for glaucoma progression or not [18–20]. Asrani [21] reported that intraocular pressure fluctuation was a risk factor for glaucoma progression, whereas Liu et al. [22] found that there was no significant difference in 24-h fluctuation of intraocular pressure between primary open-angle glaucoma (POAG) patients and normal population. Medeiros [23] and Early Manifest Glaucoma Trial (EMGT) [18] reported that long-term intraocular pressure fluctuation was not associated with glaucoma progression, whereas Advanced Glaucoma Intervention Study (AGIS) [24] showed that intraocular pressure increased by 1 mmHg, and accordingly the risks of disease progression increased 31%. The mean 24-h fluctuation of intraocular pressure in exercisers was 0.48 ± 2.22 mmHg, and that in non-exercisers was about 0.27 ± 3.58 mmHg. The 3-month long-term fluctuation of intraocular pressure was about 2.58 ± 0.96 mmHg (right eye) and 2.30 ± 0.89 mmHg (left eye) in exercisers, and that was 2.13 ± 0.94 mmHg (right eye) and 2.39 ± 1.02 mmHg (left eye) in non-exercisers.

11.1.1.5 The Mechanism of Intraocular Pressure Reduction After Exercise

Although many scholars had conducted studies on the mechanism of intraocular pressure reduction after exercise, no enough evidence was found. The more acceptable mechanisms of intraocular pressure reduction by exercise were as follows:

1. The decrease of intraocular pressure after exercise depends on the relative load rather than the absolute load [25, 26].
2. The higher the baseline intraocular pressure, the greater the decrease in intraocular pressure after exercise [27].
3. The intraocular pressure of glaucoma patients decreased significantly compared with normal population [28].
4. The older the patient, the smaller the intraocular pressure drop.
5. The amplitude of intraocular pressure reduction is proportional to the intensity of exercise, and the amplitude of intraocular pressure reduction after high-intensity exercise is about 1–4 mmHg higher than that of low-intensity exercise.
6. The decrease in intraocular pressure after exercise is considered to be the result of an increase in plasma osmolality [29].

11.1.2 Exercise and Eye-Related Serum Factors

Eye-related serum factors can be divided into five main groups with 11 serum factors, including factors related to immune regulation and effector function/nerve repair, respectively: IL-6 (interleukin-6) and TNF-a (tumor necrosis factor-α); factor related to the growth, differentiation, repair,

Table 11.1 Changes in serum factors after aerobic exercise (χ ± SD, unit: pg/ml)

n = 90	Before aerobic exercise	After aerobic exercise	*P*
HSP70	5.79 ± 2.69	6.40 ± 2.92	0.28
HSP27	12.63 ± 8.52	15.37 ± 13.17	0.21
IL-6	107.34 ± 99.49	114.31 ± 102.24	0.06
IGF-1	644.46 ± 411.35	549.21 ± 422.02	0.10
TNF-α	32.74 ± 12.39	34.51 ± 11.44	0.07
VEGF	186.71 ± 144.14	185.25 ± 139.96	0.75
NSE	7.68 ± 2.17	7.83 ± 3.26	0.74
ADP	33.00 ± 7.95	34.07 ± 11.85	0.43
ACE	1.47 ± 0.39	1.50 ± 0.46	0.71
NOS	1.89 ± 0.58	1.47 ± 0.49	0.38
GLU	14.03 ± 5.16	12.86 ± 5.34	0.31

Note: Heat-shock protein 70/27, *IL-6* interleukin-6, *IGF-1* insulin-like growth factor-1, *TNF-a* tumor necrosis factor-a, *VEGF* vascular endothelial cell growth factor, *NSE* neuron-specific enolase, *ADP* adenosine diphosphate, *ACE* angiotensin-2, *NO* NO synthase, *GLU* glutamic acid

and regeneration of nerve tissue: IGF-1 (insulin-like growth factor-1); and factor related to vascular permeability: VEGF (vascular endothelial growth factor); and factor related to nerve injury: NSE (serum neuron-specific enolase); and factors related to optic nerve protection: HSP2770 (heat-shock protein), Glu (glutamate), ACE (angiotensin-II), ADP (adenosine diphosphate), NOS (NO synthetase). The changes of all these factors before and after aerobic exercise were not obvious (Table 11.1).

11.1.3 Exercise and Ocular Blood Flow

Compared with the effect of exercise on intraocular pressure, there are fewer articles about the effects of exercise on eye blood flow, which is probably because it is difficult to get data. In the past few years, low ocular perfusion pressure has been considered as an important factor in the occurrence and development of open-angle glaucoma [30]. Exercise may decrease intraocular pressure, while blood pressure is elevated, resulting in increasing of ocular perfusion pressure. In the dynamic exercise, before the intraocular pressure increasing back to baseline, there was a short increase in ocular blood flow [31], and the pulsatile ocular blood flow was also increased [32]. The systolic blood pressure was 128.00 ± 14.98 mmHg before exercise, which was slightly reduced to 127.84 ± 13.92 mmHg after low-intensity exercise, and after high-intensity exercise significantly increased to 131.72 ± 15.69 mmHg. The diastolic blood pressure was 79.71 ± 9.95 mmHg before exercise, which was increased slightly to 79.72 ± 9.05 mmHg after low-intensity exercise, and after high-intensity exercise decreased to 76.81 ± 9.34 mmHg. It indicated that after low-intensity exercise, the systolic and diastolic blood pressure was slightly changed and the blood supply of optic nerve was stable, which was conducive to the blood supply of optic nerve. However after high-intensity exercise, both the systolic blood pressure and cardiac load increased, and diastolic blood pressure decreased; moreover, vessels were constricted, and blood supply was reduced. It has indicated that low-intensity exercise is beneficial to the eye. However, studies have showed that isometric exercise and dynamic exercise can lead to an increase in ocular perfusion pressure, but the perfusion of the entire eye remains relatively stable, suggesting that there is a self-regulation in ocular blood flow [33]. After a slight increase in blood flow, this mechanism of self-regulation begins to work when the perfusion pressure reaches more than 70% of the baseline, and then its regulatory capacity gradually reduces [34]. At present, it is not possible to distinguish the self-regulation mechanism between glaucoma patients and the normal control patients with the same age. Obviously, the increase in ocular blood flow is beneficial to glaucoma patients, which can delay the progression of glaucoma. Therefore, from the perspective of ocular blood flow regulation, the exercise seems to be harmless for glaucoma patients.

11.1.4 The Possible Harm of Exercise to the Eye

In recent years, it has been reported that the progression of glaucoma is significantly faster in open-angle glaucoma patients with high myopia [35]. For the high myopia, because of a greater reduction in intraocular pressure after exercise and its lower ocular perfusion, excessive intraocular pressure fluctuations may reduce the ocular blood supply, which can be regarded as a repeated ischemia reperfusion injury [36, 37], resulting in optic nerve injury. Therefore, for the open-angle glaucoma patients with high myopia, it is still necessary to further study whether exercise, especially high-intensity exercise, is useful or not.

In addition, young glaucoma patients in progression stage may have the problem of ischemia in the exercise, which may cause temporary blindness [38]. Intraocular pressure in patients with pigmented glaucoma was increased after exercise [39]. For these patients, exercise is not recommended.

11.2 Summary

Aerobic exercise can reduce intraocular pressure of open-angle glaucoma patients under medical treatment. A long-term and low-intensity aerobic exercise is a safe, effective, and easy method to reduce intraocular pressure, and it can improve systemic immunity and increase ocular blood flow. Therefore, aerobic exercise can be used as a supplement to existing therapies for open-angle glaucoma. However, for patients with special diseases, such as glaucoma patients with high myopia, due to increased intraocular pressure fluc-

tuations after exercise, further study was needed to clarify whether there is a risk of exercise for these patients or not.

References

1. Leighton DA, Phillips CI. Effect of moderate exercise on the ocular tension. Br J Ophthalmol. 1970;54:599–605.
2. Pasquale LR, Kang JH. Lifestyle, nutrition and glaucoma. J Glaucoma. 2009;18(6):423–8.
3. Janiszewska-Zygier A. Intraocular pressure changes after effort. Klin Oczna. 1963;33:385–9.
4. Myers KJ. The effect of aerobic exercise on intraocular pressure. Invest Ophthalmol. 1974;13:74–6.
5. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. Ophthalmology. 1991;98:301–7.
6. Qureshi IA. Effects of mild, moderate and severe exercise on intraocular pressure of sedentary subjects. Ann Hum Biol. 1995;22:545–53.
7. Schmetterer L. Glaucoma: a systemic condition. Br J Ophthalmol. 2012;96:613–5.
8. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121:48–56.
9. Qureshi IA. The effects of mild, moderate, and severe exercise on intraocular pressure in glaucoma patients. Jpn J Physiol. 1995;45:561–9.
10. Mitchell P, Hourihan F, Sandbach J, et al. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology. 1999;106:2010–5.
11. Chihara E, Liu X, Dong J, et al. Severe myopia as a risk factor for progressive visual field loss in primary open-angle glaucoma. Ophthalmologica. 1997;211:66–71.
12. Lee YA, Shih YF, Lin LL, et al. Association between high myopia and progression of visual field loss in primary open-angle glaucoma. J Formos Med Assoc. 2008;107:952–7.
13. Yang YY, Wang NL, Wu L, et al. Effect of high myopia on 24-hour intraocular pressure in patients with primary open-angle glaucoma. Chinese Med J. 2012;125(7):1282–6.
14. Yang YX, Li Z, Wang NL, et al. Intraocular pressure fluctuation in patients with primary open-angle glaucoma combined with high myopia. J Glaucoma. 2014;23(1):19–22.
15. Loewen NA, Liu JH, Weinreb RN. Increased 24-hour variation of human intraocular pressure with short axial length. Invest Ophthalmol Vis Sci. 2010;51:933–7.
16. Passo MS, Elliot DL, Goldberg L. Long-term effects of exercise conditioning on intraocular pressure in glaucoma suspects. J Glaucoma. 1992;1:39–41.
17. Senol D. Lone-term effects of mild exercise on intraocular pressure in athletes and sedentary subjects. Intern J Neurosci. 2006;116:1207–14.
18. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. Ophthalmology. 2008;115:1123–9.
19. Dayanir V, Aydin S, Okyay P. The association of office intraocular pressure fluctuation in ocular hypertension with frequency doubling technology perimetry abnormality. Int Ophthalmol. 2008;28:347–53.
20. Hong S, Seong GJ, Hong YJ. Long-term intraocular pressure fluctuation and progressive visual field deterioration in patients with glaucoma and low intraocular pressures after a triple procedure. Arch Ophthalmol. 2007;125:1010–3.
21. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134–42.
22. Liu J, Zhang X, Kripke D, et al. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. Invest Ophthalmol Vis Sci. 2003;44:1586–90.
23. Medeiros FA, Weinreb RN, Zangwill LM, et al. Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. Ophthalmology. 2008;115:934–40.
24. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627–35.
25. Ozmerdivenli R, Simsek E, Bulut S, et al. Comparison of the effects of acute and regular exercise on intraocular pressure in Turkish athlete and sedentarians. Int J Neurosci. 2006;116:351–60.
26. Harris A, Malinovsky V, Martin B. Correlates of acute exercise-induced ocular hypotension. Invest Ophthalmol Vis Sci. 1994;35:3852–7.
27. Natsis K, Asouhidou I, Nousios G, et al. Aerobic exercise and intraocular pressure in normotensive and glaucoma patients. BMC Ophthalmol. 2009;9:6–12.
28. Passo MS, Goldberg L, Elliot DL, et al. Exercise training reduces intraocular pressure among subjects suspected of having glaucoma. Arch Ophthalmol. 1991;109:1096–8.
29. Ashkenazi I, Melamed S, Blumenthal M. The effect of continuous strenuous exercise on intraocular pressure. Invest Ophthalmol Vis Sci. 1992;33:2874–7.
30. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology. 2000;107:1287–93.
31. Okuno T, Sugiyama T, Kohyama M, et al. Ocular blood flow changes after dynamic exercise in humans. Eye (Lond). 2006;20:796–800.
32. Lovasik JV, Kergoat H. Consequences of an increase in the ocular perfusion pressure on the pulsatile ocular blood flow. Optom Vis Sci. 2004;81:692–8.
33. Nemeth J, Knezy K, Tapaszto B, et al. Different autoregulation response to dynamic exercise in ophthalmic and central retinal arteries: a color Doppler study in healthy subjects. Graefes Arch Clin Exp Ophthalmol. 2002;240:835–40.
34. Riva CE, Titze P, Hero M, et al. Choroidal blood flow during isometric exercises. Invest Ophthalmol Vis Sci. 1997;38:2338–43.
35. Kaiser HJ, Schoetzau A, Stumpfig D, et al. Blood-flow velocities of the extraocular vessels in patients with high-tension and normal-tension primary open-angle glaucoma. Am J Ophthalmol. 1997;123:320–7.
36. Flammer J. Glaucomatous optic neuropathy: a reperfusion injury. Klin Monatsbl Augenheilkd. 2001;218:290–1.
37. Golubnitschaja-Labudova O, Liu R, Decker C, et al. Altered gene expression in lymphocytes of patients with normal-tension glaucoma. Curr Eye Res. 2000;21:867–76.
38. Shah P, Whittaker KW, Wells AP, et al. Exercise-induced visual loss associated with advanced glaucoma in young adults. Eye (Lond). 2001;15:616–20.
39. Gallenga PE, Mastropasqua L, Costagliola C, et al. The use of a standardized exercise as a provocative test in pigmentary dispersion syndrome. Acta Ophthalmol Scand Suppl. 1997;66:26–7.

Environmental Changes and Ocular Surface Disease

12

Qingfeng Liang, Shiming Li, and Ningli Wang

12.1 Introduction

The concept of "integrative ophthalmology," with the purpose of transferring the perspective of people from each isolated organ to the macroscopic human body, emphasizes that from the view of regarding human body as a whole, people require not only to integrate each local organ, but also to analyze the interaction between macro-environment and the body. The "environment" in this section refers to the human-centered external world, which is the material basis of the subsistence and development of human beings, and is also an important condition closely related to human health. Environmental change is bound to have impact on human life and health, especially for ocular surface tissue that is directly exposed to the external environment. In this section, the effects of air pollution, water pollution, and solid waste pollution on human health are introduced briefly. Two kinds of ocular surface diseases caused by environmental factor, that is, allergic conjunctivitis and dry eye, are mainly discussed, with comprehensive description on their epidemiological characteristics, the relationship with environment, clinical features, diagnosis, treatment, and prevention. It is expected that by a case study of ocular surface disease, the majority of ophthalmologists can understand the important role of the environment in the occurrence and development of ocular diseases, and consider the analysis of environmental factors as an important part of the diagnosis and treatment of eye diseases with the thought of "integrative ophthalmology."

With the development of modern industrialization, environmental pollution has become a global problem, with fewer and fewer days of blue sky and white clouds, and the gradual disappearing of beautiful hills and waters. From the sky to the earth, and the rivers to the sea, we can see that the soil, air, and water, which all life on earth depend on, have been polluted to varying degrees. In particular, some chemical pollution is difficult to clean up from nature in decades or even hundreds of years. In these pollutants, there are many various toxic chemicals and substances that are allergic to human body. In the field of ophthalmology, ocular surface is more sensitive to damage, leading to an increase in the incidence of eye diseases. In this section, we will discuss the relationship between environmental pollution and ocular surface disease in detail, and put forward concrete methods for prevention and treatment.

There are two definitions of environmental pollution. One refers that the substances that interfere with the self-cleaning process of natural world and are harmful to the environment and health by its chemical composition or quantity arise in the environment. The other refers to the phenomenon that the foreign matter or energy results in undesirable effects of organisms or environments. The sources of environmental pollution mainly include the following aspects: (1) the waste smoke, waste gas, wastewater, waste residue, and noise emitted by the factory; (2) the waste smoke, waste gas, noise, dirty water, and rubbish produced in people's lives; (3) the exhaust and noise emitted by vehicles (all fuel vehicles, ships, planes, etc.); (4) the water from the irrigated farmland with heavy use of fertilizers, pesticides, herbicides, and other chemicals; and (5) mine wastewater and waste residue [1].

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_12

12.1.1 Environmental Pollution and Human Health

As environmental pollution becomes increasingly more serious, many people are breathing polluted air all day long, drinking polluted water, eating agricultural products grown from polluted soil, and hearing noise. Environmental pollution is a serious threat to human health.

12.1.1.1 Air Pollution and Human Health

China's air pollution belongs to coal-type pollution, and the main pollutants are smoke and sulfur dioxide, and nitrogen oxides and carbon monoxide. These pollutants enter the body mainly through the respiratory tract, without the detoxification of the liver, which is transported directly to the whole body by blood. In addition, these pollutants also affect the body surface and ocular surface and produce certain hazards to them. This hazard can be divided into three kinds: chronic poisoning, acute poisoning, and carcinogenesis.

12.1.1.2 Water Pollution and Human Health

Rivers, lakes, and other water pollution can cause serious hazards to human health, which is mainly manifested in the following three aspects. Firstly, drinking contaminated water and eating living things in sewage can result in poisoning and even death. Secondly, the water body polluted by human and animal waste and household garbage can cause infectious diseases such as viral hepatitis and bacterial dysentery. Thirdly, some chemicals with carcinogenic effects, such as arsenic (As), chromium (Cr), and aniline in the polluted water, can accumulate in organisms and produce toxic effects.

12.1.1.3 Solid Waste Pollution and Human Health

Solid waste refers to the solid substances that are discarded in human's production and living, such as mining waste rocks, industrial waste residue, waste plastic products, and household garbage, which often contain various substances that are harmful to human health.

12.1.2 Environmental Pollution and Ocular Surface Disease

12.1.2.1 Allergic Conjunctivitis

Allergen and Epidemiological Data

Environmental pollutants contain a wide range of allergenic substances. There are a variety of allergens in our clothing, food, shelter, and transportation [2].

Clothing: chemical products used in chemical fiber and textile processing, such as dyes and softeners.

Food: pesticide residues and chemical fertilizers in food, additives in processed food, etc.

Shelter: paints, adhesives, and paint used in home decoration and furniture, cleanser, detergent, plastic products, cosmetics, so-called air cleaners, etc. and all kinds of pollutants in the air-conditioning pipe, etc.

Transportation: automobile exhaust, chemical products in in-vehicle decoration materials, etc.

Ambient air: the polluted air contains a lot of NO_2, PM2.5 particles, and other allergens.

Human beings have been living in a variety of allergens. Environmental pollution is changing much faster than human's adaptation to the environment, and the human immune system cannot adapt to the increasing changes of external environment. The body constitution in normal population is constantly being sensitized by various new allergens, and people with original allergies are in highly sensitive state, which will inevitably result in higher incidence of allergic disease.

As early as 1980s, it has reported that in the developed countries of Europe, North America, Oceania, and other states, industrial pollution is considered as one of the reasons for increased asthma patients and higher mortality in recent 20 years. There are also statistics in China, indicating that the incidence of allergic conjunctivitis has increased year by year in the last 20 years. In 1992, by the retrospective analysis of allergic conjunctivitis, it has found that the patients with a family history of allergy account for 36.1%. In 2010, a statistical analysis for the medical record data of 2012 allergic conjunctivitis patients was conducted, and the result showed that the patients with a family history of allergy accounted for 25.2%; the patients without a family history of allergy accounted for 64.7%, and 10.2% of patients were unclear. These data have changed the previous view of pathogenic factors for allergic conjunctivitis that genetic allergic constitution is the main pathogenic factor for allergic disease, but the current environmental pollution has become an important factor for allergic disease [2].

Allergic conjunctivitis is the most common type of allergic eye disease. According to statistics, more than 5% of the world's population had been hospitalized for allergic eye disease, in which the proportion of allergic conjunctivitis was more than 50%. In recent years, due to the use of eye makeup, contact lenses, heavier air pollution, and other factors, the incidence of allergic conjunctivitis has increased further.

Pathogenesis and Classification

Allergic conjunctivitis is a kind of conjunctival allergic reaction caused by contacting allergy antigen. It is type I allergic reaction mainly mediated by IgE. The normal conjunctiva and its appendage tissues contain the mast cells, each of which contains hundreds of metachromatic

granules, and has hundreds of thousands of IgE receptors in cytomembrane. When the sensitinogen (antigen) enters the conjunctiva by the way of dissolving in tear film and combines with conjunctival B lymphocyte, it will produce plasma cells, which can synthesize and release allergen-specific IgE antibody, and then these IgE antibodies will bind to the IgE receptors on the surface of the mast cells. When exposed to allergens again, these antigens will specifically bind to the IgE antibody on the surface of mast cells, leading to degranulation of metachromatic granules in mast cells, and releasing a variety of inflammatory mediators including histamine, leukotriene, prostaglandins, and chemokines, thus causing a series of chemical reactions, and producing inflammatory reaction of allergic conjunctivitis and eye irritation and itching [3].

For persons who are genetically or physically susceptible to specific antigen, when exposed to this antigen, they will suffer from allergic diseases such as rapid or delayed allergic conjunctivitis, often accompanied by allergic rhinitis and so on. Seasonal allergic conjunctivitis often occurs in young and middle-aged people, with the characteristic of rapid onset, occurring as soon as exposure to allergens. The symptoms can be relieved after escaping from the allergens. The main difference between perennial and seasonal allergic conjunctivitis is that whether the allergic symptoms are perennial or not. The contact allergic conjunctivitis has a definite contact history, such as drug or cosmetic contact history. The giant papillary conjunctivitis usually has a contact history of wearing contact lens (corneal contact lens). Vernal keratoconjunctivitis is often present in children, and usually occurs or aggravates in spring and summer. Atopic conjunctivitis is commonly seen in middle-aged men, with a history of mild allergy at early stage. Certain vernal keratoconjunctivitis and atopic conjunctivitis can produce serious corneal complications and even harm vision.

Signs and Symptoms

Unbearable itching is the main symptom for most allergic conjunctivitis patients. Moreover, it can be accompanied by conjunctival congestion, edema, mucous secretions, eyelid skin redness, and other symptoms, which are more serious when it is closer to the canthus. The patient usually has no eye pain, and also no obvious visual impairment, and the pupil reflex is normal. Some studies have shown that more than 75% of patients with allergic conjunctivitis see a doctor with main reasons of eye itching. When children often rub eyes and in case of tears and frequent blinking, maybe accompanied by the signs of allergic rhinitis, continuous sneezing, coughing, and other phenomena, we should pay attention to whether the children have got allergic conjunctivitis, and if so it is necessary to conduct timely diagnosis and treatment.

Symptoms of allergic conjunctivitis will be changed with the seasons, with ups and downs of symptoms and repeated attacks, that is to say, besides related to patients' allergic constitution, both climate change and patient's activity environment are important factors of the disease attack. In general, the symptoms can get worse in the hot and dry environment with air pollution, and more flowers and plants. Except for eye discomfort, some patients may also produce nasal allergy symptoms, that is, with the occurrence of allergic rhinitis.

Vernal keratoconjunctivitis is often present in children, and usually occurs or aggravates in spring and summer. Atopic conjunctivitis is commonly seen in middle-aged men with mild symptoms. Certain vernal keratoconjunctivitis and atopic conjunctivitis can produce serious corneal complications and even harm the patient's vision.

As for the ocular symptoms, allergic conjunctivitis in children is mainly manifested by black eye, eyelid edema, conjunctival congestion and edema, follicular and papillary hyperplasia, and corneal limbus glue hyperplasia. The severe patients may have corneal infiltration. Compared with adults, the conjunctival edema of the bulbar conjunctiva and fornix and black eye in children with allergic conjunctivitis are more clinically significant. Moreover, allergic conjunctivitis in children often has imbalance in symptoms and signs.

Diagnosis and Differential Diagnosis

Accurate and timely diagnosis is very important for symptomatic treatment of allergic diseases, which can control disease progress and reduce unnecessary damage in time.

The diagnosis mainly includes the following four aspects: (1) medical history: a clear history of allergen exposure, or an undefined allergen that occurs in a particular season, polluted environment or climate, etc.; accompaniment of other allergic diseases, which is of decisive significance for the diagnosis of atypical allergic conjunctivitis in children; previous medical history; (2) symptoms and signs, such as eye itching, redness, tearing, photophobia, palpebral conjunctival papilla, and follicle; (3) the effect of anti-allergic treatment was remarkable; (4) when necessary, cytological examination or measurement of serum IgE level can be used to diagnose allergic conjunctivitis.

This disease is mainly differentiated from a variety of infectious conjunctivitis.

Treatment

1. Physical therapy: The cold compress of the eyes can reduce local temperature and constriction of blood vessels and relieve itching, burning, and other symptoms. In patients with mild symptoms, cold compress is a convenient, quick, and effective mitigation measure.
2. Drug treatment: (1) Topical administration: Topical administration has the characteristics of rapid onset and

small side effects, and is the most common method of treatment of allergic conjunctivitis. According to the mechanism, the drugs are mainly divided into the following categories: antihistamines, mast cell stabilizer, nonsteroidal anti-inflammatory drugs, and hormone drugs. For severe patients, immunosuppressant can be used. All of the above medications should be used under the guidance of an ophthalmologist. Do not use by oneself. (2) Systemic medication: In general, oral drugs can improve compliance and are effective in most cases. The main oral drug is antihistamines, which has a lasting effect.

3. Surgery: In general, allergic conjunctivitis in children can be well relieved by drug treatment. For severe complications such as corneal macula, operative treatment can be used to scrape macula and cover the amniotic membrane, to promote the restoration of the cornea.
4. Specific immunotherapy: It is also called desensitization treatment. Clinical practice has confirmed that patients after regular desensitization treatment often benefit for the whole life, which is difficult to be achieved by general drug treatment. However, there are no standardized criteria for the allergen, and many of the allergen cannot be found, so further study for the treatment is necessary.

After avoiding allergen exposure, physical therapy, and drug therapy, most patients could get good prognosis. Because allergic conjunctivitis is a kind of disease that is caused by the combined effect of the environment and heredity, the control of environmental pollution cannot be ignored.

12.1.2.2 Dry Eye

Definition of Dry Eye and Its Relationship with Environmental Pollution

Dry eye is a kind of disease that is abnormal in the amount and quantity of tears and dynamics caused by any cause, and then results in the instability of the tear film and (or) the abnormality of the ocular surface, accompanied by eye discomfort [4]. Clinical survey has showed that dry eye is currently the most common ocular surface disease (epidemiological investigation in the United States has found that 14.4% of people over the age of 48 have dry eyes, while some data have showed that people above 65 years old with dry eyes account for 33.7% in Taiwan, China; although there is no specific epidemiological data to date in China, it is estimated that the number of patients is more than 80 million), and is also one of the most important blinding eye diseases. It is the focus and difficulty of ophthalmology in recent years [5–7].

In the 2011 annual meeting of American ophthalmology, Thomas published a study report, which showed that an increase in air pollution index increased the incidence of dry eye disease. The researchers analyzed the dry eye records of more than 600,000 patients in nearly 400 eye clinics from 2006 to 2011, and used this analytical data to compare the air pollution data in various cities over the same period. The results showed that most major cities had higher levels of air pollution, and the incidence of dry eyes increased with the increase of their pollution index (17–21%).

Cause Analysis of Dry Eye

Dry eye syndrome is a series of uncomfortable symptoms that occur due to a decrease in tear volume, or tear quality change, which is not sufficient for the eyes to be moist and lubricated. It has been clinically confirmed that with environmental pollution, such as dust, chemical pollution and especially PM2.5 particles, increasing the concentration of 10μg/m^3, the osmotic pressure of tear film will reduce 10.9 mOsm/kg, the ocular surface symptom score will increase by 8~12 points. Moreover, the MUC5AC produced by goblet cells decreases, and then dry eye disease occurs. In addition, dry eye is also related to eye surgery and history of trauma. Dry eye is commonly present in patients with systemic immune diseases such as rheumatoid arthritis and dry syndrome, and patients with diabetes. People who work in front of the computer for long hours every day and people who are used to working and living in air-conditioned dry conditions are prone to cause dry eye. The lack of sleep, mental stress, and other physiological causes can also cause the decrease of tear quality in elderly patients. Taking some hypotensive drugs and some mood stabilizers has an impact on the production of tears, such as taking chlorobenzene with an inhibitory effect on the production of tears, and taking propranolol and some current contraceptive drugs with a decrease in the production of tears [8, 9].

Symptoms and Signs

The symptoms of dry eye include eye dryness, burning, foreign body sensation, and visual fatigue, redness, stabbing pain, increased secretion, and other phenomena. Eye dryness is an early manifestation. Some of the outpatients often don't think they have dry eyes, and complain of no eye dryness, but just that they feel uncomfortable in their eyes with any stimulation, such as tearing induced by irritation of the wind, often with tears in their eyes and so on. In fact, this is the manifestation of dry eye because the reflex stimulation causes the lacrimal secretion to increase.

Clinical Examination

1. Schirmer's test: The normal level is 10–15 mm; the secretion less than 10 mm is low level, and the secretion less than 5 mm is dry eye. In the absence of ocular surface anesthesia, the secretion of the main lacrimal gland was tested. After the ocular surface anesthesia, the secretion of the accessory lacrimal gland (basal secretion) was tested. The observation time was 5 min.
2. Tear film breakup time (TBUT): The time less than 10 s indicates the instability of tear film.

3. Tear ferning test: In the patients with lack of mucous protein, such as ocular pemphigoid and Stevens-Johnson syndrome, the "fern" decreased or even disappeared.
4. Biopsy and impression cytology: The conjunctival goblet cell density of patients with dry eye was reduced, and the nucleoplasm ratio was increased, with the epithelial cell squamous metaplasia, and corneal epithelium epithelialization. By calculating the density of goblet cells in conjunctiva, the severity of the disease can be assessed indirectly.
5. Corneal fluorescein staining: Positive results represent corneal epithelial defect. The height of the lacrimal river can also be observed.
6. Rose bengal staining: The sensitivity of this staining is higher than that of fluorescein staining. The inactivating cell in the corneal and conjunctiva is stained as a positive cell.
7. Lysozyme content in tears: If the content is less than 1200 μg/ml, or lysis area is less than 21.5 mm^2, it will indicate dry eye disease.
8. Tear osmotic pressure: Tear osmotic pressure in patients with dry eyes and contact lens wear has increased by 25 mOsm/L compared with normal people. If it is greater than 312 mOms/L, dry eye can be diagnosed. This is specific and has higher early diagnostic value.
9. Lactoferrin: Before the age of 69, if it is less than 1.04 bg/ml, or after the age of 70 if it is below 0.85 mg/ml, dry eye can be diagnosed.
10. Tear clearance rate: The objective is to detect whether the tear clearance is delayed. The detection can be finished by application of fluorophotometry.
11. Tear scope plus or tear film interferometer to detect the lacrimal lipid layer: Patients with dry eye, especially patients with LTD, show abnormal lipid layer of tear film. Compared with the standard image, the severity of the dry eyes can be speculated.
12. Corneal topography: This method is used to understand the regularity of corneal surface. Dry eye patients have higher regularity parameters of corneal surface (surface regularity index and surface asymmetry index) than normal people, and the degree of increase is positively correlated with the severity of dry eyes.
13. Serological examination: This method is used to understand the autoantibodies, and the SS patients are usually positive with ANA antibodies and rheumatoid factors. This is beneficial for the diagnosis of dry eye caused by immune diseases.

Clinical Diagnosis

At present, the diagnosis criteria of dry eye have not been unified. Because dry eye is caused by abnormal quality or quantity of tear film, its diagnostic criteria should reflect not only the abnormality in quantity of tear film, but also the abnormality in quality. The diagnostic criteria proposed by Tzu betake reflect this requirement well, which are as follows: (1) dry eye symptoms, such as eye dryness, foreign body sensation, and visual fatigue; (2) positive for rose bengal staining or fluorescein staining; and (3) abnormal tear film dynamics, such as abnormal BUT (less than 5 s) and abnormal Schirmer's test (less than 5 mm). If all these conditions are met, dry eye can be diagnosed. Zhang Hancheng of China also proposed a diagnosis criterion of dry eye. He considered that with the relevant symptoms and two of the following three conditions, dry eye can be diagnosed: (a) The result of rose bengal staining is positive; (b) BUT is less than 5 s; and (c) in Schirmer's test, the secretion is less than 5 mm.

The Treatment of Dry Eye

At present, dry eye has become a common ocular surface disease and its etiology is complex. The central principle of dry eye treatment is to protect the patients' visual function, through supplementing or recovering the normal component of tears, to restore the normal anatomy of ocular surface, inhibit inflammation of the ocular surface, and eventually restore the normal anatomy and physiological function of the ocular surface and tear film. Currently, ten major drugs are clinically available for the treatment of dry eye, such as artificial tear substitute and lubricant, drugs to promote the secretion of tears, PAY receptor agonist, mucus-dissolving medicine, vitamin A agents, corticosteroids, nonsteroidal anti-inflammatory drugs, cyclosporine A, FK506 [3], and autologous serum [10]. Artificial tear replacement therapy can relatively improve the lubrication degree of ocular surface and the humidity ocular surface, and even improve eyesight. The current artificial tear has several different dosage forms, including solution, gel, and ointment. The main difference is the viscosity, composition, and whether containing preservative or not. Artificial tear with low viscosity is a first-line drug for the treatment of mild dry eye, and artificial tear with high viscosity is the drug for treatment of moderate and severe dry eye. Ointment is used for night treatment. Polyethylene glycol eye drop is a high-molecular polymer with hydrophilic and film forming, and under the appropriate concentration will be attached to the ocular surface to protect ocular surface which is similar to tears. It is used to temporarily relieve symptoms caused by eye dryness, such as burning and tingling. The studies have found that after using polyethylene glycol eye drops, symptoms of dry eye patients have improved, and the majority of patients were comfortable, with reading or watching computers for longer periods of time. It is a kind of artificial tear substitute with which the dry eye patients are more satisfied.

In the published literature, three studies specifically aimed at the effects of polyethylene glycol eye drops on TBUT. The first study was pilot study carried out by Pollard et al. The positive results of the study led Carels et al. to perform a

randomized and double-blind trial in more detail. Carels et al. compared polyethylene glycol eye drops with the products Refresh Tears and Refresh Endura, and the conclusion was that, compared with the control products, the polyethylene glycol eye drops did significantly improve TBUT after 30 min. Therefore, they concluded that the polyethylene glycol eye drops can prolong the TBUT, which may be the direct cause of the improved ocular surface staining from the polyethylene glycol eye drops reported by Christensen et al. This is similar to the findings of current study, and the author puts forward that there is a correlation between TBUT extension and ocular surface staining, because many studies have shown that continuous use of artificial tears can improve the tear film by repairing the ocular surface.

Another study by Guillon et al. [8] found that after the drop with a longer time with each measurement period of 30 min until 120 min, polyethylene glycol eye drops could significantly prolong TBUT, and control products (sodium hyaluronate) significantly extended TBUT only 120 min after the drop. As for the stability of tear film, the authors found that the incidence of the thickened lipid layer of polyethylene glycol eye drops was higher than that of sodium hyaluronate, and the difference was significant in 120 min. An increase in the thickness of the lipid layer may provide an explanation for "some substance that slows down the rate of tear clearance" put forward by Carels.

The Prevention of Dry Eye

1. Avoid "staring." Blink regularly and make sure that you can blink at least 4–5 times/min.
2. When outdoor environment is polluted, wear protective glasses or reduce going out, and avoid too long air-conditioning. Avoid airflow in your seat and place tea near your seat to increase the surrounding humidity.
3. Eat more fruits, vegetables, dairy products, fish, and other foods rich in vitamins.
4. Maintain good living habits, get enough sleep, and do not stay up late.
5. Avoid using computers continuously for a long time and pay attention to the middle rest. Usually using for 1 h, rest for 5–10 min. You can overlook or do the visual exercise when having a rest.
6. Maintain a most appropriate posture, allowing the eyes to look horizontally or slightly downward at the screen.
7. When the room is dark, turn on the fluorescent lamp to alleviate the concentrated exposure of the screen light to the eye. The ambient light should be soft, and the computer screen should be in appropriate brightness and better clarity. Moreover, the height of the desk and chair should match with the height of the computer.
8. If you don't have a lot of tears inherently and your eyes are easy to dry, you will be not appropriate for using contact lenses in front of a computer, and should wear framed glasses. For people wearing in front of a computer, it is best to use the contact lenses with high oxygen permeability.
9. For female friends, it is recommended to avoid heavy makeup.

12.2 Summary

The damage of environmental pollution to the eyes is huge, with wide involvement and high hazard level, and is difficult to control. We must do a good job in every step for the prevention and control of environmental pollution to protect our own eyes, and insist on the principle of priority to prevention, combining prevention and governance, and comprehensive treatment, and truly coordinate environmental protection and governance with economic and social sustainable development.

References

1. Zhang S. Environment and health. Beijing: Social Sciences Academic Press; 2011.
2. Xu H. Analysis of allergic conjunctivitis with dry eye in children. J Med Forum. 2010;21(5):117.
3. Gehlsen U, Cursiefen C, Steven P. Basic immunology and current therapeutic concepts in ocular allergy. Klin Monatsbl Augenheilkd. 2014;231(5):490–5.
4. The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). OculSurf. 2007;5:75–92.
5. Rahman A, Yahya K. Validity of symptoms as screening toll for dry eye. Pak J Ophthalm. 2007;23(4):198–203.
6. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the ocular surface disease index. Arch Ophthalmol. 2000;118:615–21.
7. Moss SE, Klein R, Klein BE. Prevalence and risk factors for dry eye syndrome. Arch Ophthalmol. 2000;118:1264–8.
8. Lee AJ, Lee J, Saw SM, et al. Prevalence and risk factors associated with dry eye symptoms: a population-based study in Indonesia. Br J Ophthalmol. 2002;86:1347–51.
9. Chia EM, Mitchell P, Rochtchina E, et al. Prevalence and associations of dry eye syndrome in an older population: the blue mountains eye study. Clin Exp Ophthalmol. 2003;31:229–32.
10. Schaumberg DA, Sullivan DA, Buring JE, et al. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136:318–26.

The Influence of Microgravity to Pathology and Physiology of the Eye

13

Jing Li, Weiwei Chen, Ningli Wang, and Gangwei Cheng

13.1 Introduction

An ancient saying goes that the sky is black, the earth is yellow, and the universe is vast and boundless; the sun is straight and slant, the moon may wax or wane, and the stars are interspersed in the endless space. It shows the understanding of the vast universe and desire of exploring the mysterious space for ancient Chinese. With the development of space technology, the illusory dream of space travel has come true, making humanity truly free from the gravity of the earth and step into an unpredictable vast new world. Standing in space, the earth is only like a drop in the ocean. What will happen to the structure of human body when out of the earth's "microenvironment," in which we are constantly evolving and perfectly adapting over millions of years? And which way should we take to realize the physiological function adjustment and adapt the huge change of living environment? These are problems that need to be studied and solved for the human's developing space travel. Thus, this proposal requires the researchers to inspect the "eye" in such special environment from the perspective of integrative medicine. In addition to the impact of radiation on the local part of the eye, as part of the body, the eye is bound to suffer from the secondary effects due to the changes of blood circulation of the whole body under the state of vacuum and microgravity. At the same time, through the study on the structure and function changes of the eye and body in such special environment, we are offered a unique "model" to enable us to acquire a better understanding and knowledge of the current diseases.

Space travel is an important way for mankind to explore the unknown world, unknown space, to broaden human understanding and civilization. The development of space technology is a manifestation of comprehensive national power and scientific and technological strength. The possession of space resources is also a manifestation of national strategy. At present, only the United States, Russia, and China have mastered the manned space technology. It is reported that the US National Aeronautics and Space Administration invests about 17.7 billion US dollars for the manned space technology research each year. China has vigorously developed the manned space technology since 2003, with the annual investment of about 20 billion *yuan*.

Now, China's manned space technology is still in the stage of short-term space travel (up to 15 days), while the United States and Russia have reached the longest time of 378 days in space. In the futural manned space study, humans need longer time to stay in space. At present, the MARS 500 plan has been launched internationally to simulate the human long-duration space survival in order to explore the possibility of long-duration space survival. There are many differences in the environment between the space and the earth, such as high vacuum, microgravity, and strong radiation. These differences provide us rich resources of scientific research and scientific environments; however, it will also harm the astronauts' health. Although now people can use the space suit to fight against vacuum and strong radiation, the space microgravity environment is still unavoidable in the space flight. Therefore, it is the focus issue of manned space research to study the damage mechanism of the microgravity environment to the human physiological structure and the related protection measures.

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_13

13.1.1 Overview on Space Microgravity

Space and the earth's surface environment are very different. The gravity unit is 1 G in the earth's surface, while the space is in a vacuum state, that is, 0 G. Microgravity refers to the acceleration not more than 10^{-5}–10^{-4} G caused by the gravity or other outside forces. What astronauts in space microgravity feel are completely different from that on the ground. All body organs and systems are affected by microgravity and have a corresponding pathophysiological change (Fig. 13.1).

13.1.2 The Impact of Space Microgravity on the Entire Body System

The study of National Aeronautics and Space Administration (NASA) shows that due to the lack of downward gravity, the whole body fluids will be transferred to the upper body and head, with muscle atrophy [1], bone mineral loss [2], cardiovascular dysfunction [3], vestibular and sensory organ disorders [4, 5], metabolic and nutritional system disturbance [6], immune system dysregulation [7], and frequency of occurrence of these changes related with the time of space flight, the individual's ability to adapt in a microgravity environment, and whether to take measures [8].

13.1.3 The Impact of Space Microgravity on the Eye

According to the latest study of NASA, it has showed that long-duration space flight will not only affect the bones and viscera of the whole body, but also various structures and functions of ocular tissue, having a great threat to the astronauts' ability of space operations. In addition to the increasing risk of astronauts with cataract exposure to a variety of radiation and ultraviolet in space environment, some astronauts showed fundus optic disc edema, hyperopic drift, choroidal gauffer, cotton spots, and even permanent fundus damage, which remain a year after the flight [9–11]. The abovementioned damages are collectively known as visual impairment intracranial pressure (VIIP) syndrome by NASA.

13.1.3.1 Vision

The effect of space microgravity on vision is mainly manifested as hyperopic shifts, that is, near vision decreased significantly and no obvious change in distance vision. The main cause of hyperopic shifts is the shortening of the ocular axis, which further causes the focus to be formed behind the retina when the parallel light enters the eye, and makes it unable to form a clear image of the external objects in the retina.

The distance vision increases by three diopters per 1 mm shortening of the ocular axis (Fig. 13.2).

13.1.3.2 Choroid

In the microgravity environment, systemic venous blood is transferred to the head and neck. Choroid is the blood vessel-rich tissue, including large vascular layer, medium layer, and capillary layer; therefore, it will thicken and form into folds under the force of microgravity (Fig. 13.3).

13.1.3.3 The Retina and Optic Nerve

After a long-duration space flight, a variety of fundus changes will appear in some astronauts, mainly including optic disc edema, optic nerve sheath widening, and posterior eye flattening (Figs. 13.4 and 13.5).

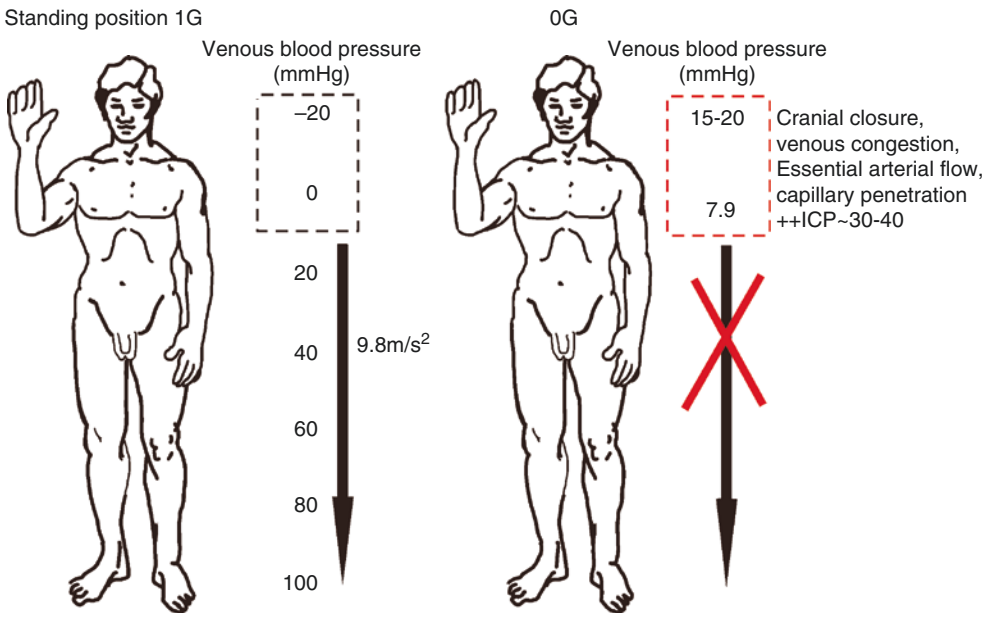

Fig. 13.1 Schematics of microgravity. Standing position, Venous blood pressure. Cranial closure, venous congestion, essential arterial flow, capillary penetration

Fig. 13.2 Hyperopic shifts. Hyperopia shift, light entering the eyeball, emmetropia, hyperopia shift, standard logarithmic visual acuity chart

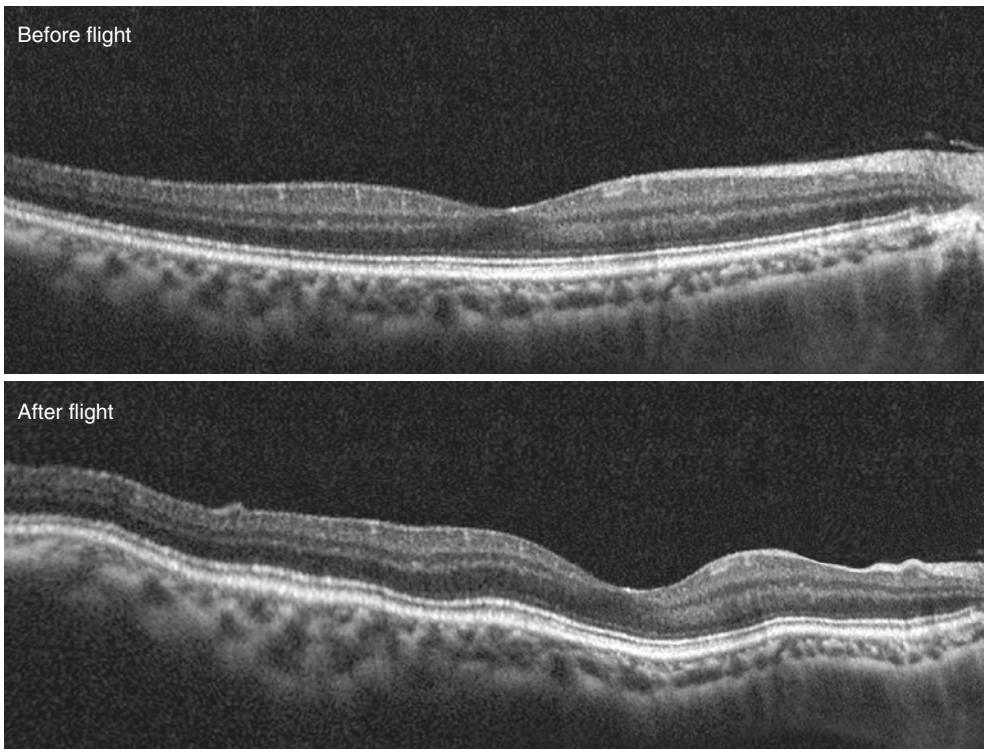

Fig. 13.3 Schematics of folding of choroid, Before flight, after flight

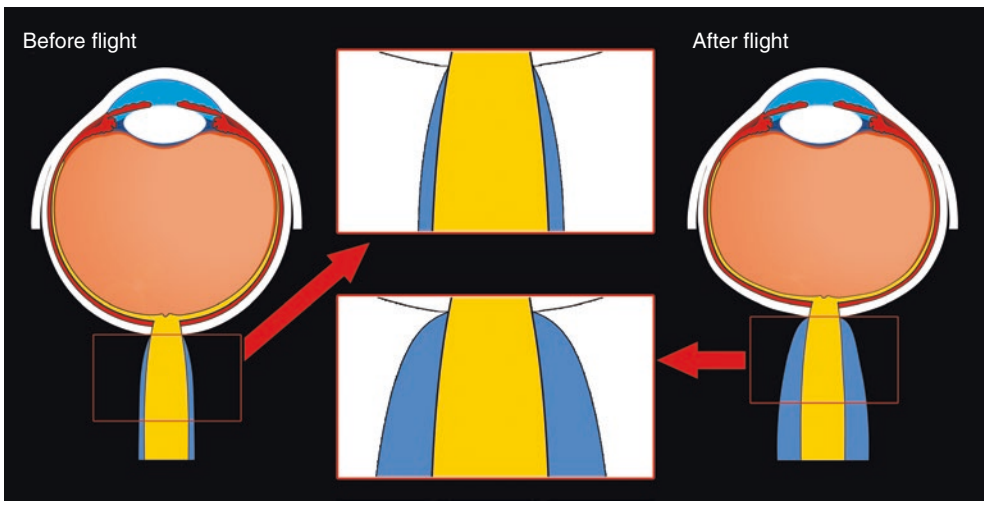

Fig. 13.4 Schematics of widening of optic nerve sheath. Before flight, after flight

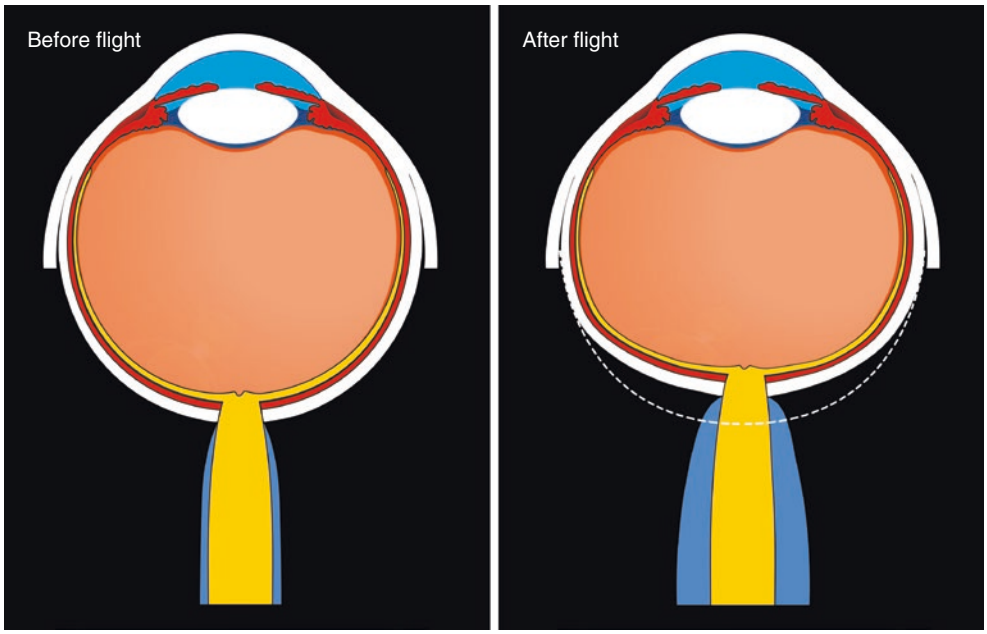

Fig. 13.5 Schematics of flattening of posterior part of the eye. Before flight, After flight

13.1.4 The Possible Mechanism for Space Microgravity Impacting Pathology and Physiology of the Eye

To date, the main causes and potential mechanisms for the occurrence of VIIP are not yet clear. Researchers have put forward various hypotheses. Kramer et al. [12] retrospectively analyzed the magnetic resonance imaging of 26 astronauts, and found that the astronauts' eyeball and brain changes were similar to the manifestation of patients with idiopathic intracranial hypertension, suggesting that elevation of intracranial pressure in microgravity may be the leading cause of the above symptoms. However, there are some researchers who propose different point of views. They have found that none of those astronauts who have damage of the eyes has chronic headache symptoms, and their eye symptoms do not conform to the intracranial pressure which is inferred via cerebrospinal fluid pressure when the flight is over. Therefore, they believed that intracranial hypertension was not the only factor of VIIP syndrome, but the microgravity-induced cephalic liquid conversion was the most important factor [11]. In addition, the increasing CO_2 concentration, high-salt diet, high-intensity resistance exercise in the flight capsule, difference of body's metabolic pathways caused by intracervical venous pressure, and genetic propensity are also considered to be associated with the VIIP syndrome [6, 10, 13].

Professor Wang Ningli and his iCOP Group in Beijing Tong Ren Hospital, Capital Medical University, have long been engaged in the study of the effect of intraocular pressure (IOP) and intracranial pressure (ICP) on the ocular structure. In their preliminary studies, it has been found that clinical normal-tension glaucoma patients may have low ICP and increasing cross-laminar pressure gradient, suggesting that different causes of cross-laminar pressure difference may lead to various optic nerve damage. When the cross-laminar forwarding pressure gradient with IOP higher than ICP increases, the characteristic glaucomatous optic nerve damage may occur, such as thinner retinal nerve fiber layer, increased optic cup, and narrowed neuroretina rim. However, when the cross-laminar retrogress pressure gradient with ICP higher than IOP increases, there will be optic nerve damages opposite to glaucoma, manifested as thickened retinal nerve fiber layer, decreased optic cup, and broadened neuroretina rim. After analyzing NASA data on visual impairment and ICP changes of the astronauts in space, the iCOP group found that astronauts' symptoms, such as optic disc edema, choroidal folds, cotton spots, and hyperopic shifts, were similar to the performance of cross-laminar retrogress pressure gradient increase. The astronauts staying in space for a long duration will have ICP elevation and IOP decrease, suggesting that astronauts' eye damages may be associated with an increase in the cross-laminar retrogress pressure gradient caused by ICP higher than IOP. It is now believed that there are two stages in the response of the human body to microgravity. The first stage is a dynamic adjustment period for several hours to days, which is an immediate effect on microgravity. The second stage is chronic adaptation period following the first stage [14], which may be related to the self-regulation and remodeling of blood vessels, as well as the dynamics of cerebrospinal fluid and aqueous humor. Mismatch of IOP and ICP eventually leads to the VIIP syndrome [10, 14].

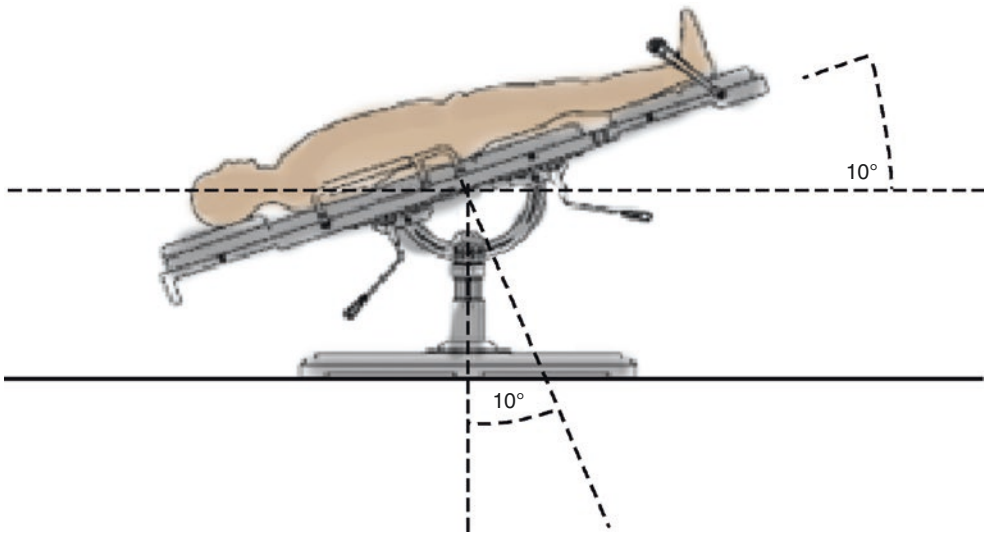

Fig. 13.6 Schematics of −10° Trendelenburg position simulating microgravity, 10°

In order to confirm the above assumption, iCOP Group has conducted a series of comparative studies. Firstly, the microgravity environment was simulated and whether the recruited subjects exhibit the same visual damages as astronauts were observed, and its potential mechanism was further explored. However, due to inevitable gravity on earth at present we only could utilize the head-down bed rest experiment to simulate space microgravity environment [13]. Since we cannot apply the presumed damage factor directly to the human body in experiment, it is imperative to find a way for such experiments to replace human beings. Because the anatomy and function of the eyeballs and nervous system are very similar to humans, and the analogies with human disease are higher than other animals, and easy to be observed, primates such as macaques become one of the ideal animal models of ophthalmic research. Macaques in the study were fixed to the −10° head-down bed rest to simulate the microgravity environment (Fig. 13.6), and to observe the IOP, fundus image, retinal nerve fiber layer, and structure of optic disc. The results confirmed that after 6-week head-down bed rest, the mean IOP was significantly increased by 4.75 mmHg (20.69%), and the average retinal nerve fiber layer thickness was significantly increased by 9.02 μm (9.31%), especially for the nasal side. In the optic disc-related parameters, the rim area was significantly increased by 15433.35 μm^2 (10.96%), but there was no significant change in the Bruch's membrane distance, the depth of the cup, and the thickness of the laminar.

From the study, it can be seen that after 6-week −10° head-down bed rest, the monkeys' IOP was significantly increased. Previous researchers have conducted a number of studies, and the results showed that it was different in IOP change for different experimental subjects, different angle of the head-down posture, or different bed rest time. In the 2-min to 48-h acute trial, the IOP was significantly increased, with the range of 2–5 mmHg [15–18], and was related to the time of head-down bed rest and tilt angle. In glaucoma patients, this phenomenon is more obvious [19]. Studies have shown that it may be associated with the changes of humoral circulation in microgravity environments, such as choroidal blood circulation being blocked and vessel hyperemia swelling, to compress the scleral tissue, causing a sudden increase in IOP, and related with the increase in surface sclera venous pressure [20]. However, in the chronic test, the test results are various. Chiquet et al. [21] performed a 7-day −6° head-down bed rest test for healthy volunteers, and the results showed that IOP was significantly reduced at the fifth and seventh days, and back to baseline in the following 2 days. In this study, the result was opposite to that in healthy volunteers in chronic head-down bed rest test, and the reason is unclear. First, we consider that it may be related to the macaque's ocular structure. The macaque in the natural life environment is accustomed to jumping between the branches. In order to adapt to this life mode, the eye vascular accommodation force and mode of macaques may be different with that of human. Second, in previous studies, the reason for the reduction of IOP may be that in long-duration bed rest test, due to venous return obstruction, especially vortex venous return obstruction, choroidal edema appears, following shallow detachment, resulting in decreased IOP. However, the macaque's long-term life habits of jumping between branches make the choroidal and sclera connection closer; as a result, it is not easy to cause choroidal detachment. Another possible explanation is that it is common for macaques to walk down on 4 ft, so the body fluid circulation has adapted to the long-duration parallel position, while the human walks upright on 2 ft, so the body fluid has adapted to the

long-duration head-up position. Thus, the change of human's blood circulation in the −6° head-down bed rest is much greater than that of macaques in −10° head-down bed rest. Macaque's blood circulation system may not be produced by chronic adaptation to −10° head-down bed rest, resulting in changes in body fluid circulation. This may be one of the possible mechanisms for increasing IOP.

In the study, the ocular fundus OCT scan was performed on the macaques in head-down bed rest, and it was found that the thickness of the retina nerve fiber layer and the rim area in macaques were significantly increased. Taibbi et al. [22] found a similar result; they observed the ocular changes of a 25-year-old Caucasian male healthy volunteer who maintained the posture of head-down bed rest for 30 days, and then measured IOP, vision, vision field, and OCT. The results showed that binocular IOP was declined by 4 mmHg, and the symmetry blind spots can be seen in the lower binocular vision field. At the same time, OCT scan revealed an increase of 19.4 μm (+5.2%) in parapapillary retinal thickness, and an increase of 0.03 mm^3 (+5.0%) in the cup volume. In this study, healthy volunteers had neither complaints of discomfort, nor clinical symptoms of papillary edema. In 6 months after the experiment, the male volunteer's eyes were re-examined and all changes were back to baseline levels. These changes were considered to be caused by a change in the body fluid circulation resulted from head-down tilt bed rest, which may be associated with insufficiency of venous valve in superior vein venous of the human body. And another possible mechanism was the cerebrospinal fluid and aqueous humor outflow adaptive adjustment caused by internal jugular vein return. But this mechanism may not appear in head-down bed rest model under a gravity field, so it partly explained the cause that the health volunteers had no complaints of discomfort. It is inferred that in our study the mechanism of increased ocular retinal nerve fiber layer thickness and rim area may be similar to that of this study. The above experiments have demonstrated that primates' simulating microgravity state can lead to the similar eye performance as astronauts, and provided a tool for the pathogenetic mechanism study of eye injuries in microgravity. Further studies will provide a powerful support for manned spaceflight technology.

13.2 Summary

In conclusion, the effect of space microgravity on the pathology and physiology of the eye is various, mainly manifested as VIIP syndrome. Its potential mechanism remains unknown. It is considered in the current mainstream theory that the microgravity environment leads to fluid hydrostatic pressure loss of blood and cerebrospinal fluid circulatory system, and then causes changes of intraocular and intracranial fluid flow, eventually resulting in mismatch of IOP and ICP, which is the most important reason of VIIP syndrome. Only with further exploration and research of the etiology and pathogenesis can effective prevention and treatment measures aiming at the cause of the disease be expected, so as to minimize the incidence of the disease as soon as possible.

References

1. Gopalakrishnan R, Genc KO, Rice AJ, et al. Muscle volume, strength, endurance, and exercise loads during 6-month missions in space. Aviat Space Environ Med. 2010;81:91–102.
2. Keyak JH, Koyama AK, LeBlanc A, et al. Reduction in proximal femoral strength due to long-duration spaceflight. Bone. 2009;44:449–53.
3. Stenger MB, Brown AK, Lee SM, et al. Gradient compression garments as a countermeasure to post-spaceflight orthostatic intolerance. Aviat Space Environ Med. 2010;81:883–7.
4. Bock O, Weigelt C, Bloomberg JJ. Cognitive demand of human sensorimotor performance during an extended space mission: a dual-task study. Aviat Space Environ Med. 2010;81:819–24.
5. Reschke MF, Bloomberg JJ, Paloski WH, et al. Postural reflexes, balance control, and functional mobility with long-duration head-down bed rest. Aviat Space Environ Med. 2009;80(Suppl 5):A45–54.
6. Smith SM, Zwart SR. Nutritional biochemistry of spaceflight. Adv Clin Chem. 2008;46:87–130.
7. Crucian BE, Stowe RP, Pierson DL, et al. Immune system dysregulation following short vs. long duration spaceflight. Aviat Space Environ Med. 2008;79:835–43.
8. Payne MW, Williams DR, Trudel G. Space flight rehabilitation. Am J Phys Med Rehabil. 2007;86:583–91.
9. Chylack LT Jr, Peterson LE, Feiveson AH, et al. NASA study of cataract in astronauts (NASCA). Report 1:Cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. Radiat Res. 2009;172:10–20.
10. Zhang LF, Hargens AR. Intraocular/intracranial pressure mismatch hypothesis for visual impairment syndrome in space. Aviat Space Environ Med. 2014;85:78–80.
11. Mader TH, Gibson CR, Pass AF, et al. Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. Ophthalmology. 2011;118:2058–69.
12. Kramer LA, Sargsyan AE, Hasan KM, et al. Orbital and intracranial effects of microgravity: findings at 3-T MR imaging. Radiology. 2012;263:819–27.
13. Pavy-Le Traon A, Heer M, et al. From space to Earth: advances in human physiology from 20 years of bed rest studies (1986–2006). Eur J Appl Physiol. 2007;101(2):143–94.
14. Watenpaugh DE, Hargens AR. The cardiovascular system in microgravity. In: Handbook of physiology: environmental physiology. New York: American Physiological Society; 1996. p. 631–74.
15. Ventura LM, Golubev I, Lee W, et al. Head-down posture induces PERG alterations in early glaucoma. J Glaucoma. 2013;22(3):255–64.
16. Kaeser P, Orgul S, Zawinka C, et al. Influence of change in body position on choroidal blood flow in normal subjects. Br J Ophthalmol. 2005;89:1302–5.
17. Longo A, Geiser MH, Riva CE. Posture changes and subfoveal choroidal blood flow. Invest Ophthalmol Vis Sci. 2004;45:546–51.

18. Xu X, Cao R, Tao Y, et al. Intraocular pressure and ocular perfusion pressure in myopes during 21 min head-down rest. Aviat Space Eviron Med. 2010;81:418–22.
19. Prata TS, De Moraes CG, Kanadani FN, et al. Posture-induced intraocular pressure changes: considerations regarding body position in glaucoma patients. Surv Ophthalmol. 2010;55:445–53.
20. Mader TH, Gibson CR, Caputo M, et al. Intraocular pressure and retinal vascular changes during transient exposure to microgravity. Am J Ophthalmol. 1993;115:347–50.
21. Chiquet C, Custaud MA, Le Traon AP, et al. Changes in intraocular pressure during prolonged (7-day) head-down tilt bed rest. J Glaucoma. 2003;12:204–8.
22. Taibbi G, Kaplowitz K, Cromwell RL, et al. Effects of 30-day head-down bed rest on ocular structures and visual function in a healthy subject. Aviat Space Environ Med. 2013;84(2):148–54.

14 Study on Generation and Outflow of Aqueous Humor from the Perspective of Organs

Chen Xin, Ningli Wang, and Gangwei Cheng

14.1 Introduction

Aqueous humor is the important content inside the eye, and plays a vital role in maintaining the morphology of the eyeball, stability of intraocular pressure (IOP), and nutrition of anterior segment tissue. In the previous studies, people were accustomed to regard the eye as an independent organ from the body. The eyeball perfusion study in vitro based upon the above logic has suggested that the aqueous humor passively drained out of the eye along with the pressure gradient between intraocular pressure and episcleral venous pressure, during which the trabecular meshwork only played the role of drainage channel. But from the concept of holistic integrative medicine, the study of any organ should not be separated from the whole body. The body's overall cycle, activity, and its interaction with the surrounding environment are closely related to the organ. Therefore, from the perspective of holistic integrative medicine, when we analyze the formation and outflow of aqueous humor from the view of the whole body regarding the eye as part of the body, we will surprisingly find that in the case of stroke volume being different, or the eyeball movement and eyelid closure, or the body position changing, the intraocular pressure will be changed instantaneously, and in a relatively long period of time the intraocular pressure is maintained in a relatively stable status. Thus we can't help associating this with the pump function of the heart, which makes blood pressure remain stable in a long term by relying on its complete anatomical structure and fine self-regulation. With re-examining the dynamics of aqueous humor, people have realized that aqueous truly drains out of the eye by a pulsatile pattern. The outflow pathway, especially trabecular meshwork pathway, plays the role of self-regulation. Therefore, people recognize that the outflow pathway of aqueous humor is a finely set, fully functioning, and precisely controlled micro-organ formed on the basis of the large system of human body.

Aqueous humor is the important content inside the eye, and plays a vital role in maintaining the morphology of the eyeball, stability of intraocular pressure (IOP), and nutrition of anterior segment tissue. Aqueous humor is always in a dynamic balance state. It is produced from the non-pigment epithelium of ciliary process by active secretion, and drains out of the eye through trabecular meshwork pathway and uvea sclera pathway, in which trabecular meshwork pathway plays a major role (nearly 90% of the aqueous humor outflow). In normal physiological state, intraocular pressure (IOP) is 15 mmHg, and episcleral venous pressure is 7–8 mmHg. Aqueous humor drains out of the eye along with the pressure gradient established by heart, through trabecular meshwork and Schlemm's canal (SC), and eventually enters into the episcleral vein. In the past, the aqueous humor was considered to flow out of the eye in a passive way, and the microstructure of the trabecular meshwork pathway was rigid during the outflow of the aqueous humor, with no occurrence of elastic deformation. In fact, the perfusion volume of the ophthalmic artery varies with the change of cardiac output. In the systolic phase, the ophthalmic arterial blood pressure is elevated, blood perfusion is increased, and the choroid is dilated, which consequently leads to reduction of intraocular volume and elevation of intraocular pressure. Correspondingly, in the diastolic phase, the ophthalmic arterial blood pressure is decreased, the blood perfusion is

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_14

reduced, and the choroid is retracted, which consequently leads to expansion of intraocular volume and decline of intraocular pressure [1]. Thus, stability of intraocular pressure depends on the autonomic regulation of local tissue, similar to the stability of blood pressure depending on autonomic regulation of effector organ in cardiac cycle. In addition, aqueous humor drains out of the eye in a pulsatile pattern. Researchers gradually recognize that TM (trabecular meshwork) pathway is not simply the "drain pipe," but a finely set, perfectly functioning, accurately regulated micro-organ.

14.1.1 The Concept of Pulsatile Outflow of Aqueous Humor

The pulsatile outflow of aqueous humor refers to the condition when IOP temporarily fluctuates, juxtacanalicular tissue (JCT)–SC area detects the IOP change and adjusts through self-transformation and deformation of fiber-plate structure of TM, thus controlling the volume of aqueous outflow and achieving the dynamic balance of IOP. In order to better understand the role of the organizational structure in the process of pulsatile outflow, we first review the maintenance of blood pressure (Fig. 14.1). The dynamic balance of blood pressure is determined by two aspects, on the one hand depending on the heart valve, acting as a one-way valve, and on the other hand relying on a stable amount of heart stroke. The maintenance of heart stroke depends on three factors, namely, normal myocardial dilatation and contraction, ventricular end diastolic volume (preload), and aortic pressure (afterload). In addition to the normal systolic and diastolic capacity of the myocardium, the maintenance of the preload and afterload depends on the precise regulation of the valve as well. Previous studies have confirmed that the pulsatile discharge process in aqueous humor can simulate the adjustment process to maintain blood pressure level; however, the structure adjustment of aqueous drainage pathway is more complex (Fig. 14.2), and the regulatory factors are also more complex (Fig. 14.3).

14.1.2 Histological Basis of the Aqueous Pulsatile Outflow

The pulsatile outflow volume of aqueous humor also depends on three factors, namely, intraocular pressure (preload), episcleral venous pressure (EVP) (afterload), and contractility and relaxation of trabecular meshwork. The maintenance of the preload and afterload relies on the valve structure to prevent the countercurrent of aqueous humor, through the morphologic observation of composition of aqueous humor in episcleral vein, firstly confirming that there is indeed the phenomenon of pulsatile outflow of aqueous humor [2–4]. Johnstone MA et al. observed the flow of aqueous humor in the episcleral vein before and after water test. It was confirmed that aqueous humor outflow volume was increased due to the elevation of IOP in the systolic period, and the aqueous outflow volume was decreased due to the blood backflow and increase of EVP in the diastolic period (Fig. 14.4). Stegmann et al. used gonioscopy to observe the filling of SC in the cardiac cycle. It was confirmed that the SC was filled with aqueous humor due to the increase of IOP in the systolic period, while in the diastolic period EVP was higher and the SC was filled with blood [4]. In this experiment, although there was blood backflow in the SC, the blood had never entered into the anterior chamber; thus it also prompted another structural which restrained the blood to flow back into the anterior chamber—the existence of the valve—and ascertained its location that limited in the SC.

A and B were images in the diastole and systole before water drinking test when intraocular pressure was 11 mmHg. C and D were images in the diastole and systole 30 min after water drinking test when intraocular pressure was 13 mmHg. E and F were images in the diastole and systole 60 min after water drinking test when intraocular pressure was 16 mmHg. Red represents vein, and blue represents aqueous humor. It can be seen that in the diastole due to the increase of venous pressure, more blood in the episcleral vein reflexed and was mixed with aqueous humor, and the episcleral vein was filled with blood. During the systole, image B showed that a large amount of aqueous humor outflew due to elevated intraocular

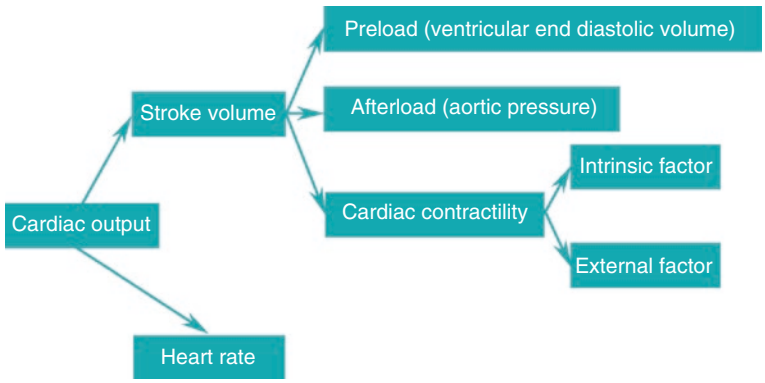

Fig. 14.1 The maintenance of blood pressure

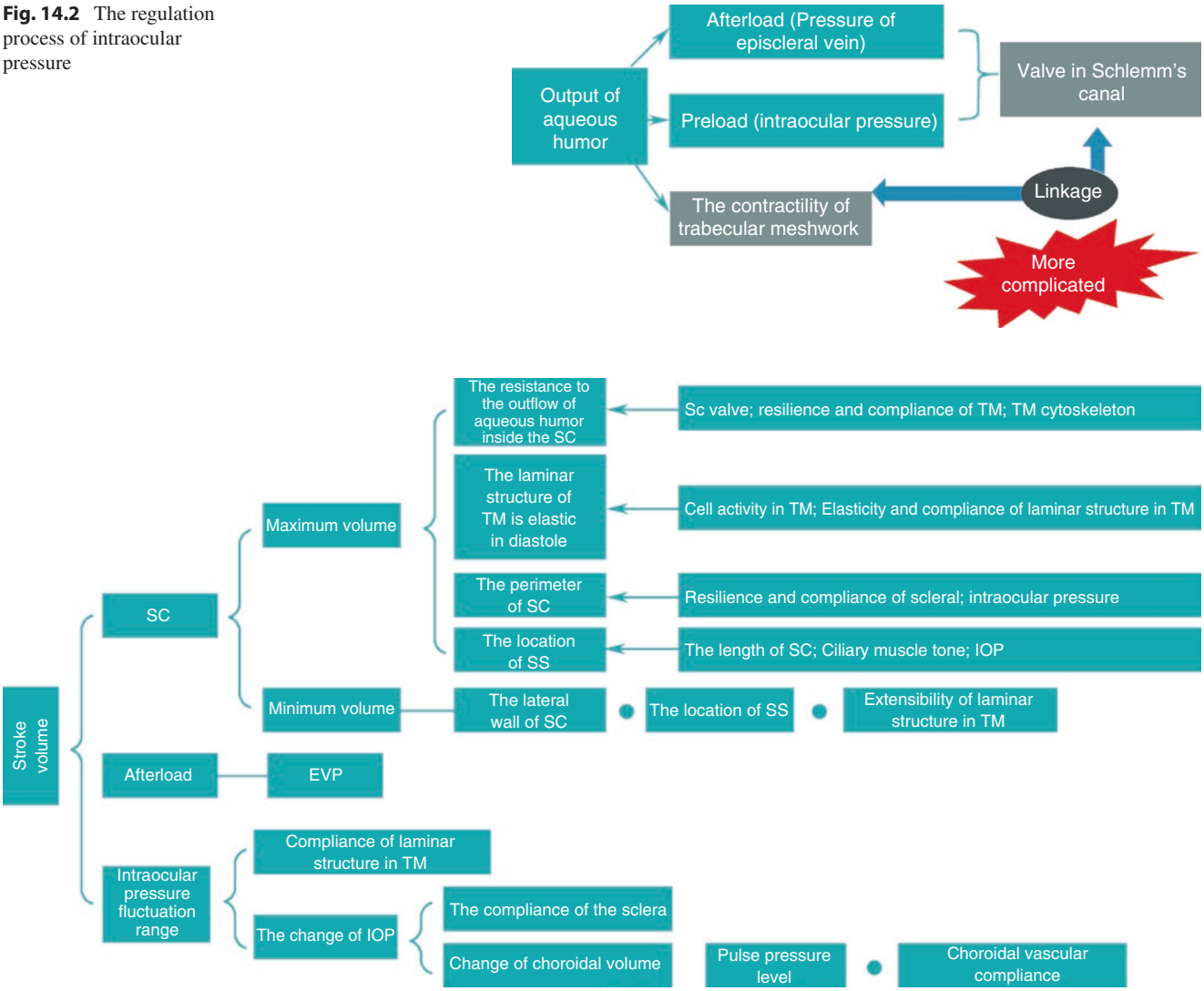

Fig. 14.2 The regulation process of intraocular pressure

Fig. 14.3 Adjustment factors of pulsating aqueous humor outflow in glaucoma patients

pressure, and part of the episcleral vein was completely filled with aqueous humor. After water drinking test, the intraocular pressure increased and the external flow of aqueous humor increased, and thus the increase of aqueous humor components in the episcleral vein occurred in both systole and diastole.

This valve structure can be observed under surgical microscopy and dissecting microscopy (Fig. 14.5) [5–7]. Under the surgical microscope, the valve is a transparent, lumen-containing cylindrical structure that spans the inner and outer walls of the SC. When the blunt separation or greater strength is applied to pull the outer wall of SC, the valve will rupture, and aqueous water will flow out from the broken end. The structure of SC valve can also be observed under light microscope [8–10]. Besides, elongation of SC valve when lens was shifted back can also be observed [10]. In terms of the matrix components, the undetermined substance in the SC valve annulus is similar to cells in the JCT region, suggesting that the SC valve not only is structurally related to the trabecular meshwork, but also has the function of transporting aqueous humor [11]. Since the valve not only has the role of one-way valve, but also involves in the liquid transport process, we believe that the maintenance of dynamic balance of intraocular pressure is more complex compared to the maintenance of blood pressure. The ultrastructure of the SC valve can be seen more clearly under electron microscopy [9].

Then, who is playing the role of compliance deformation and autonomic contraction and diastolic function similarly like myocardium, during the process of aqueous outflow? Johnstone MA et al. firstly demonstrated the compliance deformation of the trabecular meshwork in the process of intraocular pressure and EVP changes [12]. When EVP is higher than intraocular pressure, the blood flows back to the

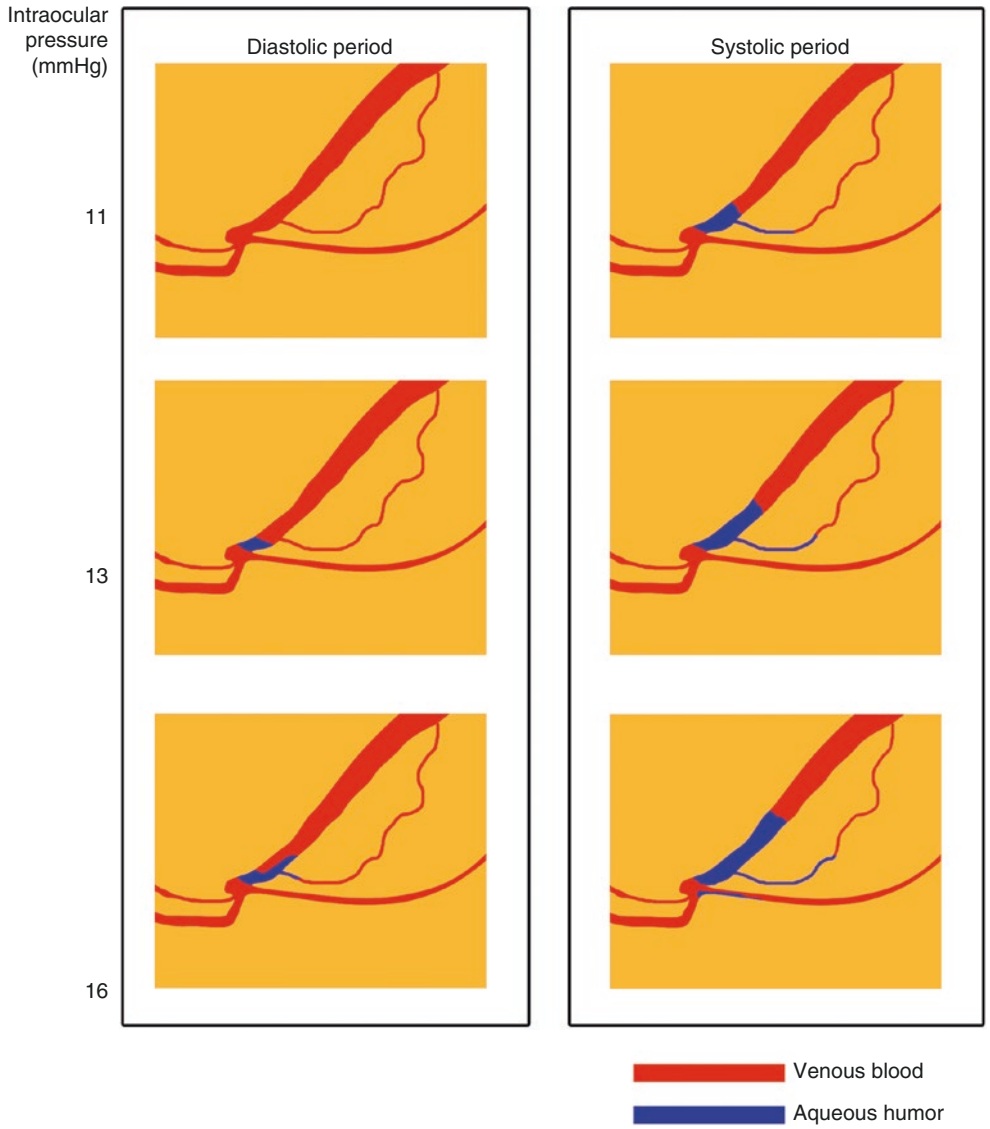

Fig. 14.4 Aqueous flow in the episcleral vein before and after water drinking test

SC, leading to the increase of SC pressure and compression of trabecular mesh plates, which consequently causes the reduction of the gap; therefore, the resistance of aqueous outflow increases and the outflow volume of aqueous humor ultimately reduces. Correspondingly, when intraocular pressure is higher than EVP, the trabecular meshwork layer will expand, and part of the trabecular meshwork will herniate into the SC, leading to the increase of gap and decrease of resistance of aqueous outflow; therefore, the outflow volume of aqueous humor ultimately increases. Meanwhile, plenty of literatures have confirmed that trabecular meshwork cells have the ability to contract, and the pharmaceutical research aiming to change the skeleton structure and contractility of trabecular meshwork cell has become a hot spot in the treatment of glaucoma [13].

From the above, we can see that the outflow of aqueous humor is a process of self-regulation. With the function of spontaneous contraction and relaxation of trabecular meshwork cell, and under the control of the SC valve, aqueous humor drains out of the eye continuously across the IOP and EVP gradient in the form of pulsation.

14.1.3 Recent Advances

Although the view of the pulsatile outflow of aqueous humor is gradually recognized and accepted, there is still lack of evidence for the pulsatile outflow of aqueous humor in the trabecular meshwork under the physiological condition of the human body. Recently, Wang RK et al. conducted a study on human eyes in vivo using phase-sensitive optical coherence tomography (PhS-OCT), and successfully observed the pulsatile motion of the trabecular meshwork in the cardiac cycle [14]. The test confirmed that in the cardiac

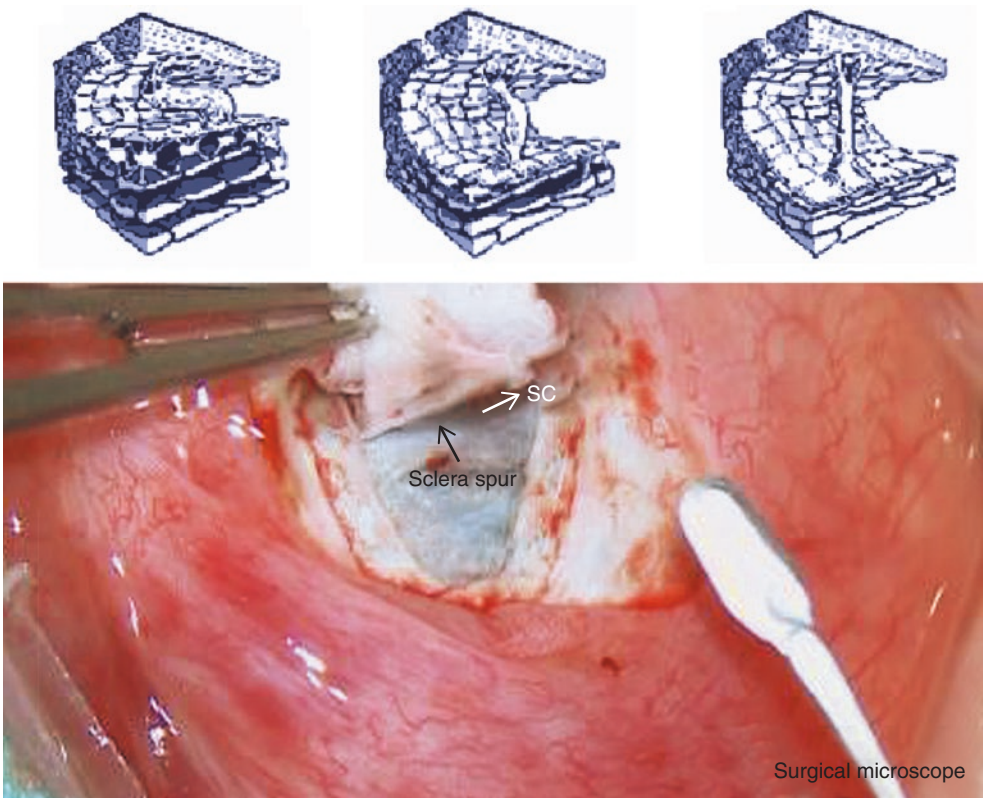

Fig. 14.5 Morphology of SC valve under surgical microscope and anatomical microscope. Reproduced with permission from Johnstone Murray A, The aqueous outflow system as a mechanical pump: evidence from examination of tissue and aqueous movement in human and non-human primates. J. Glaucoma, 2004, 13: 421–38

cycle, the frequency of trabecular meshwork motion is consistent with pulse rhythm, and delayed in the pulse. It is speculated that the pulsatile motion of trabecular meshwork is mainly due to the short-term fluctuation of intraocular pressure caused by ocular hemodynamic changes which is resulted from periodic oscillations of cardiac output. They also observed that trabecular meshwork moved toward the anterior chamber in diastolic phase, and toward the SC area in systolic phase. Furthermore, when closer to SC, the motion intensity of trabecular meshwork was stronger, and it gradually weakened in intensity when closer to the anterior chamber, suggesting that the origin of energy for trabecular meshwork motion is somewhere near the SC cavity. Besides, after the statistical analysis, the following conclusions are drawn: (1) The extent of time delay between pulsatile motion of the trabecular meshwork and blood pulse motion is shortened with the acceleration of heart rate and (2) the extent of time delay between pulsatile motion of the trabecular meshwork and blood pulse motion is shortened with the increase of age. Although the morphological changes in SC cannot be truly observed in their study, there is no doubt that with the emergence of this observation method and the improvement of future technology, we will eventually be able to observe the pulsatile outflow of aqueous humor in the living body.

Recently, Michael P. Fautsch et al. successfully used advanced micro-CT technology to observe the structure of trabecular meshwork outflow pathway and achieve 3D reconstruction of images [14]. Data analysis of the volume around the collector canal and SC can be achieved through this new technology. He believes that the anterior segment of the eye can be divided into different areas based on collector canal, since aqueous humor drains out through collector canal and eventually flows into the vein system. Under the physiological condition, only part of the collector canal functions, while the other part of collector canal serves as energy storage. In the aged and glaucomatous patients, because aqueous humor outflow pathway (SC and trabecular meshwork) belonged to part of the collector canal is incapable to complete the role of aqueous drainage the collector canal in the state of reservoir can be initiated to work. When all the drainage function depletes, aqueous outflow is unable to be maintained, and IOP of the patient will increase continuously. Therefore, he proposed the "glomerular" theory for function of collector canal and its subordinate SC and trabecular meshwork, similar to the renal filtration function. The understanding of each collector canal's area drainage will have positive meaning for the design of glaucoma surgery and selection of surgical site.

With the deepening of research, multidisciplinary cooperation, and application of knowledge of the expansion, for ophthalmologists, trabecular meshwork pathway is no longer the simple "drainage channel," but a finely set, fully functional, accurately controlled micro-organ.

References

1. Johnstone MA. Aqueous humor outflow. In: Stamper R, Lieberman MF, Drake MV, editors. Diagnosis and therapy of the glaucomas. St. Louis: Mosby; 2009. p. 25–46.
2. Goldmann H. Abfluss des Kammerwassers beim Menschen. Ophthalmologica. 1946;111:146152.
3. Goldmann H. Weitere Mitteilung über den Abfluss des Kammerwassers beim Menschen. Ophthalmologica. 1946;112: 344–6.
4. Johnstone MA. The aqueous outflow system as a mechanical pump. Int Glaucoma Rev. 2003;5:14.
5. Stegmann R, Pienaar A, Miller D. Viscocanalostomy for open-angle glaucoma in black African patients. J Cataract Refract Surg. 1999;25:316–22.
6. Smit BA, Johnstone MA. Effects of viscocanalostomy on the histology of Schlemm's canal in primate eyes. Invest Ophthalmol Vis Sci. 2000;41:S578.
7. Smit BA, Johnstone MA. Effects of viscoelastic injection into Schlemm's canal in primate and human eyes: potential relevance to viscocanalostomy. Ophthalmology. 2002;109:786–92.
8. Johnstone MA. Pressure-dependent changes in configuration of the endothelial tubules of Schlemm's canal. Am J Ophthalmol. 1974;78:630–8.
9. Johnstone MA, Tanner D, Chau B. Endothelial tubular channels in Schlemm's canal. Invest Ophthalmol Vis Sci. 1980;19:123.
10. Van Buskirk EM. Anatomic correlates of changing aqueous outflow facility in excised human eyes. Invest Ophthalmol Vis Sci. 1982;22:625–32.
11. Zhou L, Zhang SR, Yue BY. Adhesion of human trabecular meshwork cells to extracellular matrix proteins. Roles and distribution of integrin receptors. Invest Ophthalmol Vis Sci. 1996;37:104–13.
12. Johnstone MA, Grant WM. Pressure-dependent changes in structure of the aqueous outflow system in human and monkey eyes. Am J Ophthalmol. 1973;75:365–83.
13. Johnstone MA. Intraocular pressure regulation: findings of pulse-dependent trabecular meshwork motion lead to unifying concepts of intraocular pressure homeostasis. J Ocul Pharmacol Ther. 2014;30(2–3):88–93.
14. Li P, Shen TT, Johnstone M, Wang RK. Pulsatile motion of the trabecular meshwork in healthy human subjects quantified by phase-sensitive optical coherence tomography. Biomed Opt Express. 2013;4(10):2051–65.

The Eye and High Altitude

15

Yuan Xie and Ningli Wang

15.1 Introduction

High altitude is defined to begin at 2400 m (8000 ft) above sea level. Medicine recognizes that altitude above 1500 m (4900 ft) starts to affect humans. The main environment at high altitude includes low atmospheric pressure causing lower oxygen partial pressure (PO_2), decreased temperature and humidity, as well as high solar ultraviolet (UV) radiation. These special surroundings have both short-term and long-term effects on the eye.

The short-term exposure often affects visual function, refractive error, intraocular pressure (IOP), cornea and conjunctiva, retina, as well as optic nerve. The long-term exposure often causes pterygium, dry eye, and lens opacity [1].

15.2 Visual Function

15.2.1 Visual Acuity

Mild hypoxia is capable of affecting visual acuity and the photopic/high mesopic range of night vision device-aided vision. This may be due to the sensitivity to hypoxia of photoreceptors and other retinal cells [2]. Hypoxia and variations of atmospheric pressure may produce corneal edema, including changes of CCT and, correlatively, contrast sensitivity reduction. In Nepal, a small-scale study (140 children, mean age 13.9 ± 2.8 years old) found higher prevalence of myopia [3] for those that live in a high altitude. Meanwhile, 1080 porters at 2860 m altitude study found that correctable refractive errors were most prevalent to ocular diseases [4].

Lowlanders who have radial keratotomy (RK) procedure should be reminded of hyperopic shift due to corneal edema caused by hypoxia at high altitudes. Laser-assisted in situ keratomileusis (LASIK) may be a safer choice for those who ascend to high altitude. Data suggest that only a small refractive shift in the myopic direction may be present at extreme altitudes in patients of LASIK surgeries. Climbers who do not ascend beyond moderate altitudes would not experience a post-LASIK refractive shift. Post-LASIK dry eye may play a role in such environment with such low ambient humidity [5]. Therefore, native refractive error and a small refractive shift should be noticed by researchers working with native and lowlanders, respectively.

15.2.2 Color Vision

A generalized loss of color vision was found affecting both red-green and blue-yellow discrimination at an altitude of 12,000 ft. Chronic hypoxia transiently affects color discrimination, in particular tritan (blue) axis discrimination. Hypoxia acts by depressing retinal ganglion cell and s-cone cell activity [6, 7]. Decreased tritan discrimination is partly reversible upon physiological adaptation to high altitude and completely normalized upon returning to low altitude. However, a few studies revealed no changes to color vision with exposure to 3300 m in mesopic conditions. This may be below the threshold altitude for cone dysfunction. Alternatively color vision deterioration may be less significant in mesopic conditions [8].

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_15

15.2.3 Visual Fields

Moderate altitudes (7000–12,000 ft) were found to have no effects on the visual fields of subjects with glaucoma and healthy subjects [9, 10]. However, severe acute hypoxia (7620 m) reduced visual fields in particular peripheral black-and-white vision [11, 12], and the different resistance of the cone cell system (responsible for central vision) and the rod cell system (responsible for peripheral vision) functions to oxygen deprivation might account for these findings [11].

15.3 High Altitude and IOP

Several studies focused on the IOP changes at high altitude. However, the results were inconsistent and even conflicting that may be caused by differences between measuring tools and time, differences between acclimatization capacities, and so on. The results were obtained mainly by measuring the trekkers or explorers during their climb to high altitudes and pilots or healthy subjects with simulated high altitude experience in the hypobaric hypoxia chamber. The highest altitude reported could reach 9144 m. The results suggested that both lower altitude (2800 m) [13] and higher altitude (9144 m) [14] will increase intraocular pressure (IOP); However, Somner je et al. measured the IOP of the first, third, and seventh days after the lowlanders have reached 5200 m with a handheld tonometer; they also found that IOP of these lowlanders has increased, but there were no correlations between IOP and AMS [15]. Bosch MM et al. (2010) reported that at 5533 m IOP would increase but at the altitude of 6265 m IOP would decrease [16]. The intraocular pressure curve given by Pavlidis. M was more complete, and it can be seen that along with the increase of altitude intraocular pressure showed a general trend of decrease. But in the acclimatization phase (climbing below 220 m per day), intraocular pressure is somewhat recovered. Also, down to the sea-level phase, intraocular pressure is slowly returning to that of the sea level [17]. Some scholars have reported a constant trend on intraocular pressure [18] yet more researches showed that high altitudes would lead to a drop on intraocular pressure, and most of the climb is at an altitude of 4000–5000 m [19–22]. These contradictory results may due to differences on measuring tools and time, and differences on acclimatization capacities.

The increased central corneal thickness (CCT) attributed to hypoxia at high altitudes may lead to overestimation of IOP. However, some papers proposed that such increase didn't have clinical significance since it was lower than CCT changes during day and night. Meanwhile, Willmann et al. (2013) reported that the difference between anterior chamber angle (ACA) width and angle opening distance (AOD) at 4559 m was not statistically and significantly different compared with the baseline, but from the graph we can see that ACA and AOD actually decreased on the first and third days at 4559 m above sea level [23]. Hence, anterior segment changes may be involved in the mechanism of intraocular pressure changes during altitude elevation.

Aqueous humor formation dysfunction due to hypoxia and following acid-base imbalance at high altitudes may also play an important role in the mechanism of IOP change. Bosch et al. (2010) found that climbers' intraocular pressure increased when they climbed to 5533 m, and when they climbed aqueous humor was produced [16]. Pavlidis et al. found that from 2286 to 5050 m, the mean value for IOPs in the right eyes dropped by 76.7%. During the descent phase (to 3600 m) in the next 2 days, the right eye pressure increased by 18.46% (median) at this stage. When the daily climbing distance exceeded 220 m, IOP decreased a median of 1.29 mmHg (8.2% of the initial IOP) per day, whereas when they climbed less than 220 m/day, their IOP increased by a mean value of 9.9% per day. This is contributed to acid-base disturbance according to them. Hyperventilation due to hypoxemia during ongoing ascents would induce decrease in arterial CO_2 pressure followed by increased blood and cerebral spinal fluid pH values. Respiratory alkalosis caused in this way is responsible for IOP decrease in the ascent stage. Furthermore, during the acclimatization period, renal compensation for respiratory alkalosis involves an increase in HCO_3^- excretion in order to return to normal pH value ($CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$); the whole process is catalyzed by carbonic anhydrase (CA). CA also exists in the ciliary body epithelium cells, catalyzing the reaction responsible for aqueous humor production. This is the mechanism responsible for increased IOP value during ascents, and returning to baseline after acclimatization [14–17]. Meanwhile, increased aqueous humor outflow can cause IOP changes at high altitude. Reduced superior scleral vein pressure due to low temperature [24] and increased outflow of aqueous humor, like pneumatic trabeculoplasty [20], may be another reason for decreased IOP value at high altitude.

One can observe from the gross structure that optic nerves were surrounded with abundant cerebrospinal fluid which creates unneglectable intracranial pressure (ICP) at the point where the nerves enter the orbit, and thus one can correlate ICP and IOP values in a research as Salmon (1996) did in his paper [25]. Hence, IOP has proved its value as a noninvasive and portable clinical index to monitor AMS and HACE attributed to ICP at high altitude. Previous researchers reported that increased IOP correlated with symptoms and diagnosis of HACE and AMS [26, 27], and others reported that reduction of IOP is correlated with AMS scores [22]; these were the only ones that reported the relation between IOP and ICP in clinical practice. Whether or not introducing

IOP as a proper index for ICP is still a debatable subject. Although correlation between IOP and ICP is significant, different explanations made it hardly usable [28].

Patients with intravitreal gas injection should be advised not to attend high-altitude activities like air traveling as the low atmospheric pressures encountered can cause expansion of the gas volume and thus result in dangerous elevation of IOP [29–36].

15.4 Ocular Surface

15.4.1 Tear Film

Dry eye symptoms were reported to be more common in the native residents at high altitude than in the temporary residents. The prevalences of dry eye symptom showed in previous studies are 52.4% in Tibet, China, and 54% in Ladakh, India [37, 38]. Environmental factors at higher altitudes like lower humidity may increase tear film evaporation which in turn increases film osmolarity and patients develop dry eye syndromes independent of aqueous film deficiency. Other factors like wind and temperature may also accelerate the process of dry eye syndromes by destabilizing tear film and enhancing tear breakup [39].

15.4.2 Conjunctiva

Short-time UV radiation exposure may create photoconjunctivitis and photophthalmia. Photoconjunctivitis manifests as conjunctival congestion and watering from eyes, while photophthalmia appears in a form of generalized ocular discomfort followed by pain, photophobia, and foreign body sensations. They are often transient and resolved without sequelae [40]. Pterygium due to long-term UV radiation also showed a higher prevalence at high altitude than at plains [41, 42].

15.4.3 Cornea

CCT increases in a statistically significant manner for lowlanders when they ascend to a higher altitude [13, 20]; it is the result of high altitude-related hypoxia. The cornea may undergo a metabolic shift to anaerobic metabolism which yields extracellular metabolic by-products, causing a hydration pressure shift in the extracellular stromal spaces, causing increased CCT. CCT may also have correlation with AMS-C scores. Measuring CCT in doubtful cases could give an indication as to whether the person is susceptible to AMS [43]. However, unlike the lowlanders that have a temporarily increasing CCT value when they ascend to high altitude, the inhabitants have thinner CCT at such heights. However the differences are mainly caused by ethnic reasons, although the effect of environment cannot be ruled out [44].

15.4.3.1 Pupil

Initial pupil diameter was significantly reduced while contraction velocity (CV) of the light reaction was increased on all days measured at 4559 m. Schultheiss reported that pupil parameter changes did not relate to scores of AMS [45]. However, Wilson reported a reduction in both pupil aperture change (PAC) and CV within 1 h of arrival at high elevation of 3450 m or slower arrival at 3500 m, respectively. While the correlation of hypoxia with these pupil dynamics may be because of a direct hypoxic effect, other causal factors cannot be excluded. For instance, rising intracranial pressure can cause compression of parasympathetic oculomotor nerve fibers [46]. Moreover, some literatures indicate hypoxia disinhibition of parasympathetic E-W nuclei which leads to pupil contraction. Given that pupil dynamics was used as a measure of neurological function as a part of the Glasgow Coma Scale, further study of pupil dynamic variation at high elevation is of clinical significance.

15.4.3.2 Lens Opacity

The prevalence of cataract was reported to be 4.05 times higher at high altitude as compared to Kathmandu valley [47]. Overall prevalence of lens opacities in Tibet (4000 m) was 60% times higher than in Beijing (44 m). Lhasa (3658 m) also showed significantly more prevalence than in Shaoxing (15 m) [48]. Ultraviolet radiation exposure is regarded as a risk factor for cataract, especially the cortical cataract. The absorption of solar radiations by lens results in photochemical reactions and formation of reactive oxygen species (including singlet oxygen), which may damage all cellular components (lipids, proteins, DNA) and cause lens opacity [48, 49]. However, actual sunlight exposure is also important for the prevalence of cataract [40].

15.5 High-Altitude Retinopathy (HAR)

The findings of HAR commonly include increased tortuosity and dilation of retinal vessels, retinal hemorrhages (HARH), cotton wool spots, and papilledema [50, 51]. Retinal blood vessels are shown to be engorged and tortuous in lowlanders ascending above 2500 m. Hemorrhages have been reported in 56% of people ascending above 5000 m; although the risk correlates well with increasing altitude, macular involvement is rare. Vitreous hemorrhages, cotton wool spots, and papilledema are seen in severe cases. The overall incidence of pap-

illedema at high altitude reported in the previous literatures was 59–79%. Wiedman M et al. (1999) have classified HAR into four grades. Grade I: A. dilated retinal veins, B. hemorrhages up to one disc area; grade II: A. moderately dilated retinal veins, B. hemorrhages up to two disc areas; grade III: A. advanced dilated retinal veins, B. (1) hemorrhages up to three disc areas, (2) paramacular hemorrhage, or (3) vitreous hemorrhage, minor; grade IV: A. engorged retinal veins, B. (1) hemorrhages over three disc areas, (2) macular hemorrhage, (3) vitreous hemorrhage, major, or (4) papilledema [52].

The mechanism underlying HAR remains unclear. Retinal vasodilation and increased capillary permeability secondary to hypobaric hypoxia are suspected to cause hemorrhages [51]. Mullner et al. reported that retinal vascular dysregulation with increase in all hemodynamic parameters may attribute to changes in HAR [53]. It is also suggested, like other hypoxia-induced retinal diseases (e.g., von Hippel disease, proliferative diabetic retinopathy, retinopathy of prematurity, and glaucoma), that hypoxia inducible factor 1α (HIF-1 α), a heterodimeric transcription factor, could be the master switch mediating the changes in HAR [54]. The pathophysiological mechanism accounts for mild tissue edema after exposure to hypoxia including two controversial hypotheses, vasogenic edema or cytotoxic intracellular edema. Increased permeability and capillary pressure due to hemodynamic changes, in the eye, may be due to increased blood flow at high altitude and cause vascular edema. Otherwise, cytotoxic intracellular edema has been described for the brain in MRI studies at normobaric hypoxia due to reduced axonal transport. Respective MRI studies and measurements of ONSD do not provide evidence that increased ICP contributes to papilledema. However, our recent research found that at simulated high altitudes, increased rim area and radial peripapillary capillary (RPC) were correlated with decreased intraocular pressure (IOP) and increased ICP (unsubmitted). The results inferred that translaminar cribrosa pressure constitutes IOP and ICP may have effect on capillary flow density and axon transplant which, in turn, leads to increased RPC and rim area.

As we all know vessels seen in fundus may be a mirror of the systemic vessels, especially the brain's. Whether retinal hemorrhages are associated with AMS or HACE has been of interest for many scholars. Houston and Wiedman reported a correlation between high-altitude retinal hemorrhage and altitude illness or HACE in a group of mountaineers during an expedition to Mount Everest [52, 55]. Nevertheless, Clarke and Duff doubted that the appearance of isolated retinal hemorrhages should be considered as a warning sign of HACE [56]. Barthelmes et al. indicated that HARH was not associated with cerebral symptoms secondary to severe AMS or imminent HACE [57]. Schommer et al. found no microhemorrhages in the brain of both healthy subjects and subjects suffering from AMS [58] in whom HARH may be quite frequent. Given previous literatures there was no strong evidence that the appearances of HARH should not be considered as a biomarker of HACE development.

It is well documented that high-altitude hypoxia can lead to an increase in cerebral [59] and subsequently retinal blood flow [60] with distension of cerebral and retinal veins. Wilson found that retinal vessel distension has a positive correlation with headache burden during trekking lasting for several days at 5300 m [61, 62]. Bosch et al. reported a correlation between increase of retinal venous diameter and AMS scores when pooling the data from all altitudes [60]. Since there is correlation between cerebral and retinal engorgement, they proposed that retinal venous distension is due to cerebral outflow capacity limitation, which may account for headache at high altitude and possibly AMS [61]. However, a simultaneous assessment of retinal vessel distension and headache or AMS found no correlation of retinal diameter increase with either headache or AMS score at 4559 m [55, 61, 63]. To date, the retinal and cerebral vessels have only been reported upon the level of large arterials. Our recent studies found that retinal microvascular changes associated with Lake Louise Questionnaire Score (LL-score) both at simulated and real high altitude. The results indicated a possible biomarker for AMS or HACE in the eye and further large sample studies were to be launched in the future.

Bosch reported a few ODS with increasing altitude, which was paralleled by increasing AMS-C scores during ascent. However, Willmann et al. found no correlation between any quantitatively assessed parameter of the optic disc and simultaneously assessed AMS scores at 4559 m [64]. Therefore, whether optic disc swelling can predict severe AMS or immense HACE is still in discussion.

15.6 Optic Nerve Sheath Diameter (ONSD)

Increasing ONSD at high altitudes has had a strong positive correlation with more severe symptoms of AMS but a weak relationship with mild and moderate ones [65–68]. These findings do not support for the presence of increased ICP in mild-to-moderate AMS. However, high individual variation has limited the utility of sonography as a diagnostic tool [69]. Thus, advanced methods measuring optic nerve subarachnoid space area (ONSASA) may reduce the individual variation and perfect this method as a tool to predict ICP [70].

To sum up, altitude-related environments, in particular hypoxia and higher UV radiation exposure, will bring a series of pathology changes in eye. Higher prevalence of pterygium, cataract, and myopia were found in the residents who lived in plateau area. With regard to lowlanders who ascend to high altitude, there may be some short-term effects on eye but most of them will experience almost complete resolution without any sequelae unless they ascend to

extreme heights. Many eye symptoms, such as IOP, HAR, and ONSD, have correlation with altitude-related illness such as AMS and HACE. However, whether these indexes can predict and monitor altitude illness is still in discussion. Further studies on the mechanisms of altitude-related eye changes and the sensitivity of ophthalmology factors as indexes predicting altitude-related diseases still need to be conducted.

References

1. Grimm C, Willmann G. Hypoxia in the eye: a two-sided coin. High Alt Med Biol. 2012;13(3):169–75.
2. Vecchi D, et al. Visual function at altitude under night vision assisted conditions. Aviat Space Environ Med. 2014;85(1):60–5.
3. Adhikari S. Myopia in school children from high mountain region of Nepal. Nepal J Ophthalmol. 2013;5(2):246–9.
4. Gnyawali S, et al. Ocular morbidity among porters at high altitudes. Nepal J Ophthalmol. 2017;9(18):30–6.
5. Kohnen T. Effects of refractive surgery in extreme altitude or space. J Cataract Refract Surg. 2012;38(8):1307–8.
6. Willmann G, et al. Effects on colour discrimination during long term exposure to high altitudes on Mt Everest. Br J Ophthalmol. 2010;94(10):1393–7.
7. Schatz A, et al. Attenuation of S-cone function at high altitude assessed by electroretinography. Vis Res. 2014;97:59–64.
8. Davies AJ, et al. Changes to colour vision on exposure to high altitude. J R Army Med Corps. 2011;157(1):107–9.
9. Fulk GW, West RW, Nakagawara VB. Effect of simulated altitude on the visual fields of glaucoma patients and the elderly. Optom Vis Sci. 1991;68(5):344–50.
10. Yap MK, et al. Effects of exposure to simulated altitudes on visual fields, contrast sensitivity, and dazzle recovery. Aviat Space Environ Med. 1995;66(3):243–6.
11. Horng CT, et al. Visual fields during acute exposure to a simulated altitude of 7620 m. Aviat Space Environ Med. 2008;79(7):666–9.
12. Ho TY, et al. High-altitude retinopathy after climbing Mount Aconcagua in a group of experienced climbers. Retina. 2011;31(8):1650–5.
13. Karakucuk S, et al. Changes in central corneal thickness, intraocular pressure, and oxidation/antioxidation parameters at high altitude. Aviat Space Environ Med. 2012;83(11):1044–8.
14. Karadag R, et al. The effect of short-term hypobaric hypoxic exposure on intraocular pressure. Curr Eye Res. 2008;33(10):864–7.
15. Somner JE, et al. What happens to intraocular pressure at high altitude? Invest Ophthalmol Vis Sci. 2007;48(4):1622–6.
16. Bosch MM, et al. Intraocular pressure during a very high altitude climb. Invest Ophthalmol Vis Sci. 2010;51(3):1609–13.
17. Pavlidis M, et al. Intraocular pressure changes during high-altitude acclimatization. Graefes Arch Clin Exp Ophthalmol. 2006;244(3):298–304.
18. Baertschi M, Dayhaw-Barker P, Flammer J. The effect of hypoxia on intra-ocular, mean arterial, retinal venous and ocular perfusion pressures. Clin Hemorheol Microcirc. 2016;63(3):293–303.
19. Willmann G, et al. Effect of high altitude exposure on intraocular pressure using Goldmann Applanation tonometry. High Alt Med Biol. 2017;18:114.
20. Nebbioso M, et al. Hypobaric hypoxia: effects on intraocular pressure and corneal thickness. Scientific World Journal. 2014;2014:585218.
21. Bayer A, et al. Intraocular pressure measured at ground level and 10,000 feet. Aviat Space Environ Med. 2004;75(6):543–5.
22. Cymerman A, et al. Intraocular pressure and acclimatization to 4300 M altitude. Aviat Space Environ Med. 2000;71(10):1045–50.
23. Willmann G, et al. Impact of acute exposure to high altitude on anterior chamber geometry. Invest Ophthalmol Vis Sci. 2013;54(6):4241–8.
24. Ortiz GJ, et al. Effect of cold air on aqueous humor dynamics in humans. Invest Ophthalmol Vis Sci. 1988;29(1):138–40.
25. Salman MS. Can intracranial pressure be measured non-invasively? Lancet. 1997;350(9088):1367.
26. Casperson KJ, Freer L. Increased intraocular pressure measured by portable tonometry is a specific indicator of high altitude cerebral edema. Lawrence: Wilderness & Environmental Medicine (Allen Press); 2008.
27. Chatterjee SK, Chakraborty A. Intraocular pressure changes and mountaineering--preliminary observations and possible application. J Assoc Physicians India. 2001;49:248–52.
28. Sheeran P, Bland JM, Hall GM. Intraocular pressure changes and alterations in intracranial pressure. Lancet. 2000;355(9207):899.
29. Noble J, et al. Evaluating the safety of air travel for patients with scleral buckles and small volumes of intraocular gas. Br J Ophthalmol. 2014;98(9):1226–9.
30. Brosh K, Strassman I, Seelenfreund M. High intraocular pressure in four vitrectomized eyes with intravitreal C3F8 without high altitude travel. Eye (Lond). 2014;28(7):892–4.
31. Amini R, et al. Computational simulation of altitude change-induced intraocular pressure alteration in patients with intravitreal gas bubbles. Retina. 2011;31(8):1656–63.
32. Ferrini W, Pournaras JA, Wolfensberger TJ. Expansion of intraocular gas bubbles due to altitude: do meteorological factors play a role? Klin Monatsbl Augenheilkd. 2010;227(4):312–4.
33. Silvanus MT, et al. Visual loss following intraocular gas injection. Dtsch Arztebl Int. 2008;105(6):108–12.
34. Polk JD, et al. Central retinal artery occlusion by proxy: a cause for sudden blindness in an airline passenger. Aviat Space Environ Med. 2002;73(4):385–7.
35. Kokame GT, Ing MR. Intraocular gas and low-altitude air flight. Retina. 1994;14(4):356–8.
36. Mills MD, et al. An assessment of intraocular pressure rise in patients with gas-filled eyes during simulated air flight. Ophthalmology. 2001;108(1):40–4.
37. Gupta N, et al. Prevalence of dry eye at high altitude: a case controlled comparative study. High Alt Med Biol. 2008;9(4):327–34.
38. Lu P, et al. Dry eye syndrome in elderly Tibetans at high altitude: a population-based study in China. Cornea. 2008;27(5):545–51.
39. Willmann G, et al. Exposure to high altitude alters tear film osmolarity and breakup time. High Alt Med Biol. 2014;15(2):203–7.
40. Jha KN. High altitude and the eye. Asia Pac J Ophthalmol (Phila). 2012;1(3):166–9.
41. Malekifar P, et al. Risk factors for pterygium in Ilam Province, Iran. J Ophthalmic Vis Res. 2017;12(3):270–4.
42. Shrestha S, Shrestha SM. Comparative study of prevalence of pterygium at high altitude and Kathmandu Valley. J Nepal Health Res Counc. 2014;12(28):187–90.
43. Bosch MM, Barthelmes D, Merz TM, et al. New insights into changes in corneal thickness in healthy mountaineers during a very-high-altitude climb to Mount Muztagh Ata. Arch Ophthalmol. 2010;128(2):184–9.
44. Patyal S, et al. Corneal thickness in highlanders. High Alt Med Biol. 2017;18(1):56–60.
45. Schultheiss M, et al. Pupillary light reaction during high altitude exposure. PLoS One. 2014;9(2):e87889.
46. Dattani RS, et al. Pupil dynamics in hypoxic conditions: Caudwell Xtreme Everest results. High Alt Med Biol. 2014;15(3):422–3.
47. Shrestha S, Shrestha SM, Gurung A. Comparative study of prevalence of cataract at high altitude and Kathmandu Valley. J Nepal Health Res Counc. 2016;14(33):81–4.

48. Delcourt C, et al. Lifetime exposure to ambient ultraviolet radiation and the risk for cataract extraction and age-related macular degeneration: the Alienor Study. Invest Ophthalmol Vis Sci. 2014;55(11):7619–27.
49. Wang Y, et al. The relationship between the disability prevalence of cataracts and ambient erythemal ultraviolet radiation in China. PLoS One. 2012;7(11):e51137.
50. McFadden DM, et al. High-altitude retinopathy. JAMA. 1981;245(6):581–6.
51. Willmann G, et al. Retinal vessel leakage at high altitude. JAMA. 2013;309(21):2210–2.
52. Wiedman M, Tabin GC. High-altitude retinopathy and altitude illness. Ophthalmology. 1999;106(10):1924–6; discussion 1927
53. Mullner-Eidenbock A, et al. High-altitude retinopathy and retinal vascular dysregulation. Eye (Lond). 2000;14(Pt 5):724–9.
54. Arjamaa O, Nikinmaa M. Oxygen-dependent diseases in the retina: role of hypoxia-inducible factors. Exp Eye Res. 2006;83(3):473–83.
55. Frayser R, et al. Retinal hemorrhage at high altitude. N Engl J Med. 1970;282(21):1183–4.
56. Clarke C, Duff J. Mountain sickness, retinal haemorrhages, and acclimatization on Mount Everest in 1975. Br Med J. 1976;2(6034):495–7.
57. Barthelmes D, et al. Delayed appearance of high altitude retinal hemorrhages. PLoS One. 2011;6(2):e11532.
58. Schommer K, et al. Hemosiderin deposition in the brain as footprint of high-altitude cerebral edema. Neurology. 2013;81(20):1776–9.
59. Brugniaux JV, et al. Cerebrovascular responses to altitude. Respir Physiol Neurobiol. 2007;158(2–3):212–23.
60. Bosch MM, et al. New insights into ocular blood flow at very high altitudes. J Appl Physiol (1985). 2009;106(2):454–60.
61. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. Lancet Neurol. 2009;8(2):175–91.
62. Wilson MH, et al. Cerebral venous system and anatomical predisposition to high-altitude headache. Ann Neurol. 2013;73(3):381–9.
63. Willmann G, et al. Missing correlation of retinal vessel diameter with high-altitude headache. Ann Clin Transl Neurol. 2014;1(1):59–63.
64. Willmann G, et al. Update on high altitude cerebral edema including recent work on the eye. High Alt Med Biol. 2014;15(2):112–22.
65. Fagenholz PJ, et al. Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: evidence for increased intracranial pressure. J Appl Physiol. 2009;106(4):1207–11.
66. Lawley JS, et al. Optic nerve sheath diameter is not related to high altitude headache: a randomized controlled trial. High Alt Med Biol. 2012;13(3):193–9.
67. Sutherland AI, et al. Optic nerve sheath diameter, intracranial pressure and acute mountain sickness on Mount Everest: a longitudinal cohort study. Br J Sports Med. 2008;42(3):183–8.
68. Kanaan NC, et al. Optic nerve sheath diameter increase on ascent to high altitude: correlation with Acute Mountain sickness. J Ultrasound Med. 2015;34(9):1677–82.
69. Keyes LE, Paterson R, Boatright D. Optic nerve sheath diameter and acute mountain sickness. Wilderness Environ Med. 2013;24(2):105–11.
70. Liu H, Yang D, Ma T, et al. Measurement and associations of the optic nerve subarachnoid space in normal tension and primary open angle glaucoma. Am J Ophthalmol. 2018;186:128–37.

Part IV

Systemic Tumors and Eye Tumors

A Review of Retinoblastoma from the Perspective of Integrative Medicine

16

Bin Li and Xiao Zhang

16.1 Introduction

Retinoblastoma (RB) is a common primary intraocular malignant tumor in children. The retinoblastoma gene (RB gene) is the first tumor-suppressor gene found in humans. It has been confirmed that there are abnormalities of the RB pathway in all human tumor cells. Throughout the history of retinoblastoma research, material changes have happened in the pathogenesis and treatment concept of RB for more than half a century, which include the following: (1) It was previously considered that the formation of retinoblastoma is due to the absence of function of RB1 tumor-suppressor gene. Related research published by "Lancet Oncology" in 2013 has shown that the activation of MYCN proto-oncogene can also lead to its occurrence. (2) It was considered that the eyeball removal and external radiation therapy are the two cornerstones of RB therapy in traditional treatment. However, in recent years, the individualized comprehensive treatment of chemical volume reduction combined with local therapy has gradually become the first-line treatment.

The unification of whole body and local organs, as well as macroscopic and microscopic fields, is advocated in integrative medicine. The macroscopic problem in RB is how to effectively reduce its incidence and mortality, and improve the quality of life, while in terms of the microscopic level researches include the susceptibility and tolerance of the disease, and the causal relationship between human body and environmental changes. There are a large number of questions that need to be answered, such as how to deeply explain the pathogenesis of RB in the genetic level; if the new discovery of etiology could establish a new gene screening or treatment pattern; and how to effectively evaluate the risk factors of RB metastasis and assess the prognosis by cytogenetic features or histopathological changes. As for ophthalmologists, through the concept of integrative medicine and based on multidisciplinary cooperation, it will still need a long-term hard work to normalize the retinoblastoma diagnosis and treatment model, and to establish the regional treatment center in China.

Retinoblastoma (RB) is the most common intraocular malignant tumor in children, and is the second pediatric malignant tumors next to leukemia. 90% of RB cases have onset before the age of 3 years, with monocular or binocular involvement. The two eyes can be attacked successively or simultaneously. RB is prone to intracranial metastasis and systemic metastasis.

The incidence of RB in newborn babies in the United States is about 1/16,000–1/34,000. In the United Kingdom, according to the statistical data from 1969 to 1980, the incidence of RB in live births is about 1/15,000–1/20,000 [1]. At present, it still lacks statistical data of large sample in China. In 1980, Shen Fumin reported that the incidence of RB in Shanghai was about 1/11,800–1/23,160. The rate of blindness caused by RB accounts for about 5% in children diseases that caused blindness, and this rate in malignant tumor among children under 5 years old is about 6.1% [2]. There is no significant ethnic, regional, and gender differences for this tumor. Survival rate of RB is different greatly in the world, which can reach 95% in the developed countries, while the average rate is only about 50% in the whole world. In China, the survival rate of bilateral RB is about 30%, and that of unilateral RB is about 50%. With the development of medicine and the advent of various comprehensive treatment methods, the survival rate of RB children has improved greatly. According to statistical data of large sample from children in Beijing Tongren Hospital, the survival rate of RB can reach more than 80%.

There are about 350 new cases of RB each year in the United States, and the number is about 5000–8000 in the

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_16

whole world. According to the analysis of data from the United States and the calculation of the Western population, there are about 1000 new cases of RB in China every year. In recent years, the incidence of RB has a rising trend [3]. The survey data of large sample from Beijing Tongren Hospital [4] showed that the average age of onset is 23 months. The proportion is about 29%, 64%, 84%, and 96% within the age of 1 year old, 2 years old, 3 years old, and 5 years old, respectively. For the difference of disease laterality, the average age of onset is about 15 months in bilateral RB, and in unilateral RB it is about 27 months. In children with a family history of RB, unilateral cases account for 7%, and bilateral cases account for 35%, genotypic cases account for 40%, and non-genotypic cases account for 60%. From these data, bilateral multifocal tumors account for 100% in genotypic RB, while the unilateral cases account for about 15%. RB has a relatively high rate of spontaneous regression.

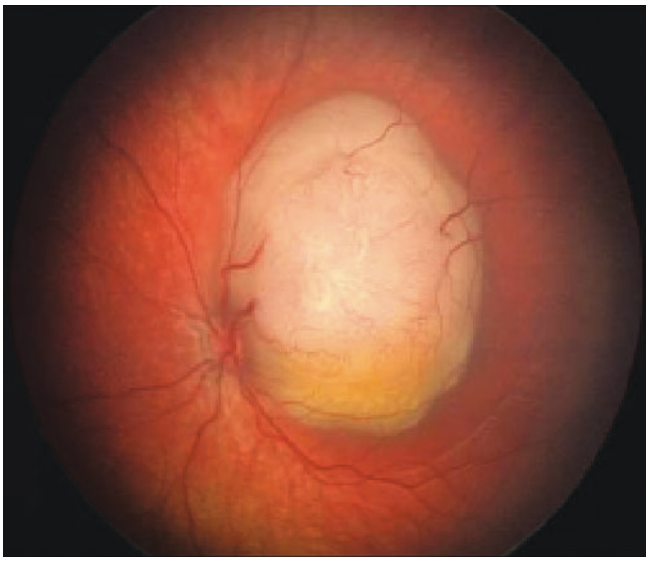

Fig. 16.1 Endogenous retinoblastoma. The tumor is located in the posterior pole, just beside the optic nerve, and grows into the vitreous cavity involving the macular center

16.2 Etiology and Pathogenesis

At least two mutational events are required for RB initiation. Genotypic RB is a mutation in germ cells with simultaneous mutation in somatic cells (retinal cells), while non-genotypic RB refers to two mutations in the same retinal somatic cells. About 40% of cases are genotypic, which are genetically inherited by parents of RB patients or mutant gene carriers, or caused by mutations in the reproductive cells of normal parents. This type is autosomal dominant inheritance, mostly bilateral, with typically multiple tumor foci of the retinal, and may be accompanied by a second tumor of elsewhere in the body. 60% of RB cases are non-genotypic type, which are due to the mutation of the patient's own retinal cells. This type is generally not genetic, has an onset relatively late, and has often unilateral involvement with only a single lesion of the retina, and the occurrence of a second tumor is less likely.

Studies have confirmed the site and type of RB gene mutation. RB gene is located in the long arm of chromosome 13, zone 1 band 4. It is found that RB gene deletion or inactivation is the key to tumorigenesis, and thus further puts forward the theory of tumor inhibition.

16.3 Growth Pattern of RB

The growth patterns of RB include endogenous and exogenous. Tumors that occur in the inner nuclear layer of the retina are endogenous type. This kind of tumor grows into the vitreous cavity and is more likely to be found (Fig. 16.1). There are white masses of different sizes in the vitreous cavity, just as a large number of floating snowball. Exogenous RB originates from the outer nuclear layer of the retina and grows under the retina. It is easy to invade the choroidal tissue earlier. Retinal detachment without holes often occurs in this type of RB, and differential diagnosis particularly needs to be made between exogenous RB and Coats disease.

Clinical stage of RB: According to the clinical process, RB can be classified into four periods including intraocular period, glaucoma period, extraocular period, and systemic metastasis period. Early stage of RB is not easy to be detected by parents, and tumors are often found when visual impairment such as white pupil (Fig. 16.2) and strabismus occurs. By slit-lamp biomicroscope examination, white gray floating seeds of tumor can be found in the anterior chamber, and sometimes tumor cell colonies can be detected at the inferior of the anterior chamber, and that is called pseudo-hypopyon (Fig. 16.3). For the older RB children patients with atypical presentation, pompon-like or snowball-like pseudo-nodules are seen on the iris surface. In the glaucoma period, the tumor grows constantly so that the intraocular volume continues to increase. When glaucoma happened with elevated intraocular pressure, the pseudo "bull-eye" appearance could be detected (Fig. 16.4).

Extraocular period of RB is a serious outcome. The tumor cells transfer to the intracranial area mainly through the lamina cribrosa and optic nerve (Fig. 16.5). In addition, tumor cells can also invade the choroid tissue (Fig. 16.6), and transfer through the scleral catheter, leading to systemic metastasis. The systemic metastases can occur at any stage of RB in clinical practice. If the tumor is present on or around the optic nerve head, even if the tumor is relatively small, tumor cells can also spread and metastasize along the optic nerve before the stage of glaucoma. In terms of RB metastasis pathways, tumor cells transfer through the optic nerve or supraorbital fissure into the intracranial area in most of the

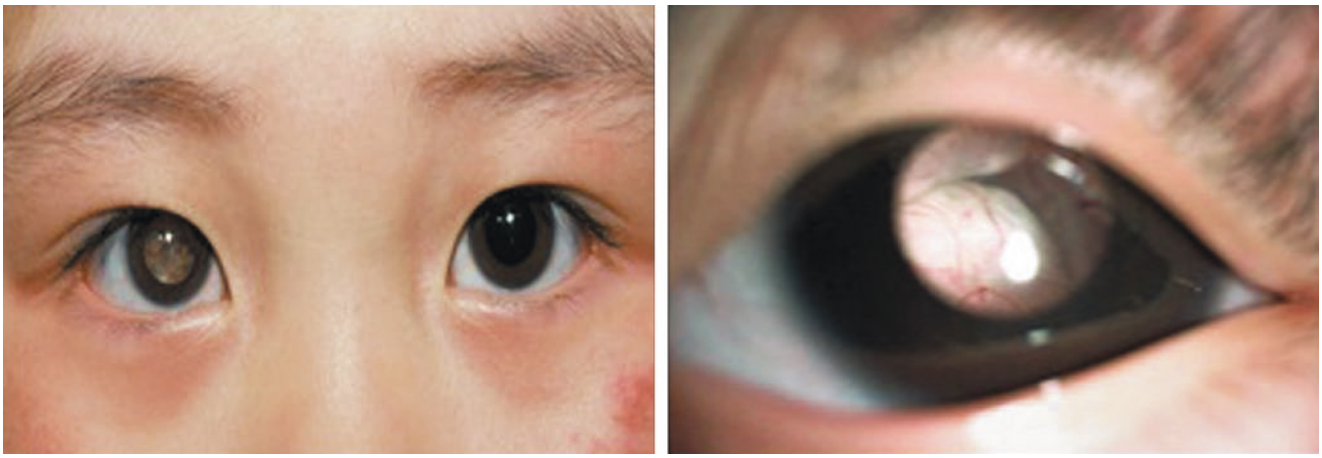

Fig. 16.2 Retinoblastoma. The clinical manifestation is white pupil. Abnormal retinal vessels can be observed on the surface of the tumor under slit-lamp microscope examination

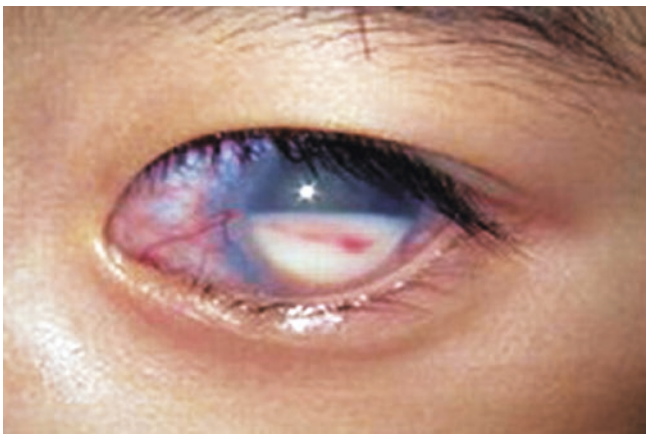

Fig. 16.3 Pseudo-hypopyon. Pseudo-hypopyon could be observed when retinoblastoma grows anteriorly and invades the anterior chamber

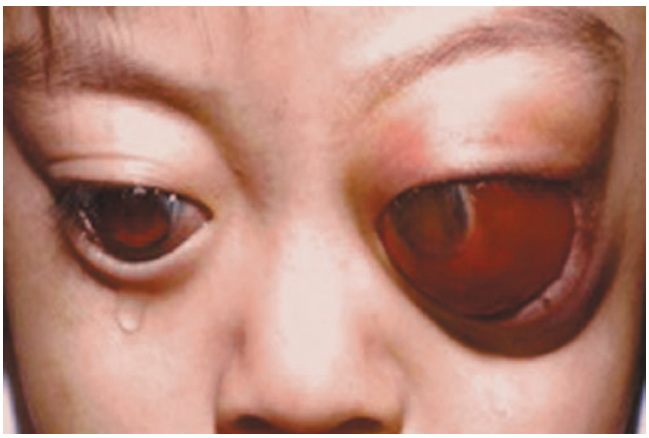

Fig. 16.4 The glaucoma period of retinoblastoma. It can penetrate the scleral catheter into the orbit and form a giant tumor leading to proptosis

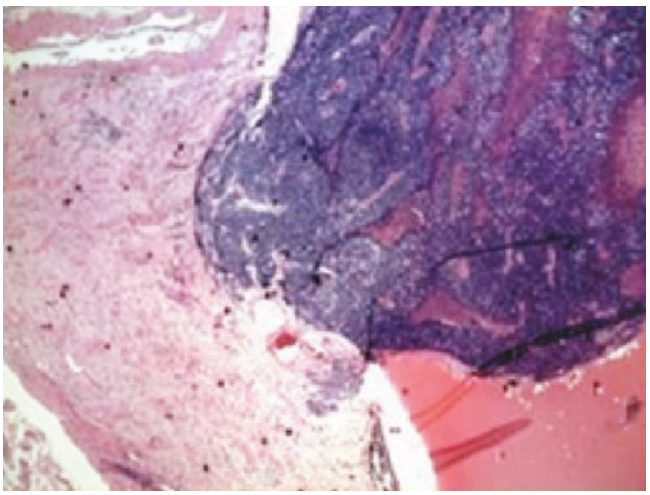

Fig. 16.5 Exogenous retinoblastoma. The optic nerve is invaded by retinoblastoma, and tumor cells transfer to the intracranial area through lamina cribrosa

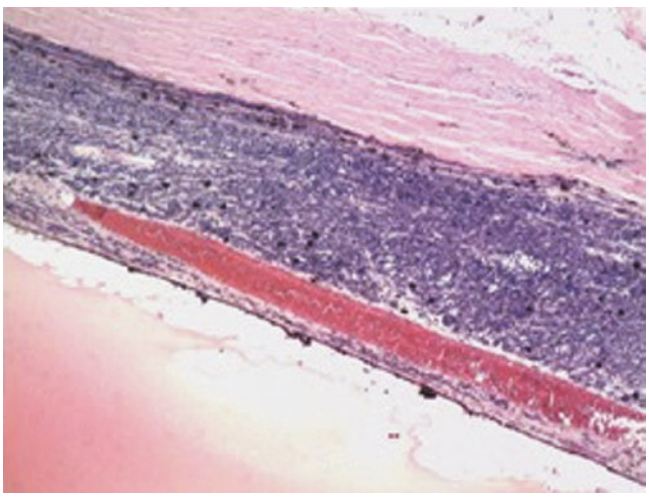

Fig. 16.6 Extensive choroid is invaded by retinoblastoma, and the maximum diameter is ≥3 mm

cases; they can also transfer through the scleral catheter to the bone and liver or other organs of the body, and sometimes they metastasize through the lymph node.

16.4 Auxiliary Examinations

Through the B-scan ultrasound and color Doppler ultrasound examination, the size of the tumor can be measured and the tumor calcification can be detected. The high-density mass in the eye ball, typical calcified plaque, and optic nerve thickening can be found by imaging examinations, such as CT and MRI scanning. For the fundus fluorescein angiography (FFA), the tumor is visible by fluorescent staining in the arterial phase, and this phenomenon is obvious in the venous phase when the fluorescence appears delayed to subside, so FFA has a certain diagnostic value. At present, FFA has been used abroad as a supplementary examination for the diagnosis of RB. But it is not the first choice of examination in our country, because most of the patients are too young. In recent years, Retcam fundus examination has opened a new era for the diagnosis and treatment of RB. According to the tumor location, size, invasive area, and subretinal exudate, the tumor stage of IIRC is determined, and then the course of treatment is confirmed.

16.5 Histologic Types of RB

Histologic types of RB mainly include undifferentiated type and differentiated type. Tumor cell of the undifferentiated type usually has large and densely arranged nucleus, manifesting as bare nucleus with almost no cytoplasm. This type appears less differentiated with high malignancy, but it is sensitive to radiotherapy. The differentiated type, also known as the neuroepithelial type, is formed by the tumor cells of "9 + 0" structure (that is, rosette-like structure) that is close to the retinal tissue structure. The tumor cells of this type are differentiated better than those of the undifferentiated type in appearance, with relatively small nucleus and certain cytoplasm. This type appears highly differentiated with relatively low malignancy, but it is not sensitive to radiotherapy. It is important to note that metastasis can also occur in the differentiated type of RB.

International classification of RB: With the development of chemical reduction therapy, that is, chemotherapy combined with local treatment, the traditional Reese-Ellsworth (RE) Classification of RB for radiotherapy is no longer able to adapt to new needs. In the 1990s, the external radiation has been unable to serve as the preferred treatment for RB, and chemical reduction therapy has become the main treatment method. As a result, in the United States Linn Murphree et al. proposed a new international staging for RB, in order to better guide clinical treatment and evaluate prognosis. Participating countries include the United States, Canada, France, Sweden, and Mexico. In 2005, a total of 27 centers in the world including Beijing Tongren Hospital attended the workshop and demonstrated the guidance role of international staging of RB in its chemotherapy. In the international staging of RB scheme, RB is divided into five levels, including stages A, B, C, D, and E. The degree of risk is very low, low, moderate, high, and extremely high from stage A to stage E, respectively.

- Stage A: Whether basal diameter or height of the tumors is less than 3 mm. The tumor is confined to the retina and located further than 2 PD from the foveola and 1 PD from the optic disc.
- Stage B: All disseminated tumors confined to the retina, without vitreous cavity or subretinal seeding.
- Stage C: Disseminated local lesions, with minimal local subretinal or vitreous cavity dissemination.
- Stage D: Diffuse lesions, with significant subretinal or vitreous cavity dissemination.
- Stage E: The risk is extremely high. The tumor causes damage to the anatomy or functions of the eye, and this kind of damage cannot be mitigated. Appearance of any one or more of the following signs can be classified as this stage, including tumor bulge touching the lens, neovascular glaucoma, tumor infiltrating the anterior vitreous, diffuse infiltrating retinoblastoma, opaque media from hemorrhage, cornea cruenta, tumor necrosis with aseptic orbital cellulitis, and phthisis bulbi.

Diagnosis of RB: Before the diagnosis of RB, it is important to make differential diagnosis with several white pupil-related diseases, including ROP, Coats disease, congenital cataract, retinal detachment, endophthalmitis, astrocyte hamartoma, and myelinated nerve fibers.

Postoperative pathology: It is very important to make histopathology examination after enucleating eyeball. The following structures should be observed carefully: lamina cribrosa, post-laminar optic nerve, and removal margin of optic nerve, choroidal tissue, and pigment epithelium layer of retina (RPE). According to the extent of optic nerve invasion, RB is divided into four grades internationally. Grade I: Tumor invasion involves anterior optic nerve head. Grade II: Tumor invasion involves lamina cribrosa. Grade III: Tumor invasion involves post-laminar optic nerve, but the stump of the optic nerve is not affected. Grade IV: Tumor invasion involves the removal margin of optic nerve. Grades I–III are more common in RB cases. It is reported that the mortality rate in 814 cases of RB is 10% in Grade I, 29% in Grade II, 42% in Grade III, and 78% in Grade IV. Even if the

tumor invasion in Grade I only involves the anterior optic nerve head, the mortality rate still reaches 10%, which exactly shows the importance of adopting early interventional chemotherapy.

16.6 Histopathological Risk Factors of RB

Histopathological risk factors of RB include the tumor invasion involving post-laminar optic nerve, wide range of choroid, sclera, and anterior segment, as well as that the tumor breaks through the eyeball to outside. Large-scale or significant choroidal invasion, more than one tumor lesions connected together, the maximum diameter of the tumor, or the scope of its violation greater than or equal to 3 mm all these are key criteria of high-risk factors [5, 6]. In addition, the study of Kaliki S summarizes the indications of adjuvant chemotherapy [7]: tumor invasion of the anterior chamber, a large range of choroidal invasion, post-laminar optic nerve invasion, and focal posterior choroidal invasion accompanied by any degree of optic nerve involvement.

16.7 Treatment Principles of RB

When treating RB patients, the priority is to save lives, followed by the retention of the eyeball, and retention of vision. The treatment concept for RB includes early detection, early consultation, early treatment, and individualized integrated treatment. At present, the treatment of RB in China is mainly adopted eyeball enucleation, and supplemented by chemotherapy. Modern RB treatment concept is to treat the tumor while focusing on the preservation of children's vision. Local treatment is performed for small intraocular tumors, including cryotherapy, photocoagulation, plaque radiotherapy, transpupillary thermotherapy (TTT), etc., and eyeball enucleation is performed for larger tumors. Exogenous retinoblastoma should undergo surgery and chemotherapy, and external radiation is supplemented if necessary. Adjuvant chemotherapy is required for the patients with exogenous tumors, intraocular tumors with high-risk factors of recurrence and metastasis, as well as tumors with intracranial spread or distant metastasis. In recent years, with the introduction of gene therapy and stem cell therapy, combined with traditional Chinese medicine treatment, the treatment of retinoblastoma, including the survival rate of children, has a certain degree of improvement.

Recently, in some Euramerican developed countries, by the combined application of multidiscipline and individualized integrated treatment program, the 5-year survival rate of intraocular RB children has reached 95%. In the future clinical work of ophthalmology, in order to help more RB children get rationalized and standardized treatment, and to further improve the survival rate of children and quality of life, we need to conduct multidisciplinary collaboration including ophthalmology, pediatrics, oncology, and ophthalmic pathology, and to carry out multicenter collaborative clinical research.

For retinoblastoma treatment, in order to fully understand our national conditions, we should learn from foreign advanced treatment experience, and make efforts to establish a rationalized and standardized therapeutic norm suitable for China's national conditions, in order to further improve the survival rate and the quality of life of RB children.

References

1. Abramson DH. Retinoblastoma in the 20th century: past success and future challenges the Weisenfeld lecture. Invest Ophthalmol Vis Sci. 2005;46(8):2683–91.
2. Qian J. Some problems should be paid attention to in the treatment of retinoblastoma. Ophthalmology. 2009;18(6):367–9.
3. Li Y, Fen G, Yi Y. Research status and prospect of retinoblastoma in China. Chin J Ophthalmol. 2004;40(4):217–9.
4. Bai S, Ren R, Shi J, et al. Retinoblastoma in the Beijing Tongren Hospital from 1957 to 2006: clinicopathological findings. Br J Ophthalmol. 2011;95(8):1072–6.
5. Chantada GL, Dunkel IJ, de Dávila MT, et al. Retinoblastoma patients with high risk ocular pathological features: who needs adjuvant therapy? Br J Ophthalmol. 2004;88(8):1069–73.
6. Suryawanshi P, Ramadwar M, Dikshit R, et al. A study of pathologic risk factors in postchemoreduced, enucleated specimens of advanced retinoblastomas in a developing country. Arch Pathol Lab Med. 2011;135:1017–23.
7. Kaliki S, Shields CL, Rojanaporn D, et al. High-risk retinoblastoma based on international classification of retinoblastoma: analysis of 519 enucleated eyes. Ophthalmology. 2013;120(5):997–1003.

The Integrative Thinking of Uveal Melanoma

17

Wenbin Wei and Xiao Zhang

17.1 Introduction

With an overview of the ophthalmic diseases, eye tumors may be one of the most suitable areas for the concept of integrative medicine. In recent years, through macro- and micro-interdisciplinary communication, the diseases are explored at different levels of histology, cytology, and molecular. As a result, great changes have taken place in the understanding of pathogenesis, diagnosis, treatment, and prevention of tumor, which mainly reflect in three aspects:

1. With the development of pathology, imageology, vitrectomy techniques, and cytogenetics, the problem of difficulty to make differential diagnosis of certain diseases has been solved.
2. In the treatment field, the treatment method mainly composed of eye enucleation has been replaced by individualized integrated treatment, improving the quality of life of patients.
3. With the development of cytogenetics, more reliable objective indicators are provided for the assessment of disease prognosis.

The changes of diagnosis from difficulty to easy, treatment from eyeball removal to retention, and prognosis from untreatable to partially treatable have showed the extreme importance of emphasizing and insisting multidisciplinary and multilevel integration of integrative medicine in the scientific thinking of cancer treatment.

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17.2 Uveal Melanoma Overview

Uveal melanoma is the most common primary intraocular malignant tumor in adults. So far, its exact etiology is unclear. The disease is related to race, and the incidence among Caucasians is about 150 times than that of black people [1]. The disease is also associated with other diseases of the eye, such as patients with ocular melanosis or skin melanosis, in whom the incidence of uveal melanoma is relatively high. The incidence of uveal melanoma is also high in the patients of multiple choroidal pigment nevus [2]. In addition, genetic predisposition and environmental factors are also related to the occurrence of the tumor. UV radiation has much to do with skin melanoma, but in places with more sunlight the incidence of uveal melanoma is not high, which may be related to genetic factors [3].

17.3 Clinical Diagnosis of Uveal Melanoma

In recent years, greater progress has been made in the clinical diagnosis of uveal melanoma. For example the advances in imaging diagnostics, acupuncture biopsy, and diagnostic vitrectomy all are valuable diagnostic tools in clinical diagnosis and differential diagnosis [4], especially for choroidal nevus, choroidal hemorrhage, choroidal hemangioma, choroidal metastases, choroidal melanocytoma, and retinal pigment epithelium (RPE) tumors. Clinically, it is difficult for us to distinguish these lesions from melanoma, but since these diagnostic tools have been used we can perform a commendable differential diagnosis. As shown in Fig. 17.1, a case of choroidal melanoma, through this wide-angle fundus fluorescein angiography, we can understand that the imaging features are different in different intraocular tumors, which is very meaningful for us to differentiate these tumors.

As for the ultrasound diagnosis, ocular ultrasound diagnosis has important value in the differential diagnosis of choroidal tumors. In particular, we have recently carried out some contrast-enhanced ultrasonography for intraocular tumors, and found that the contrast-enhanced ultrasonography is of great

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_17

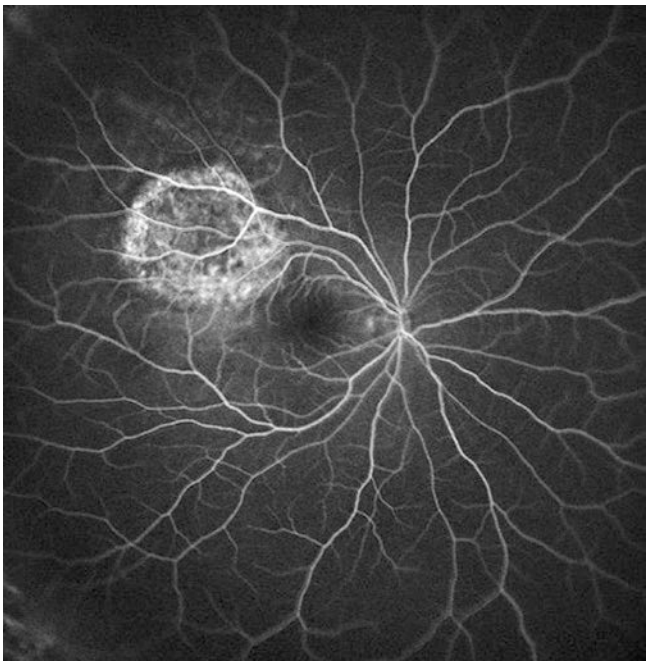

Fig. 17.1 Choroidal melanoma revealed by wide-angle fundus fluorescein angiography

importance in the differential diagnosis of intraocular tumors, especially very useful in the identification of true tumors or pseudo-tumors, benign tumors, or malignant tumors [5].

Without doubt, MRI is also very characteristic in the identification of uveal melanoma, and especially MRI enhanced scan is very valuable in the identification of a part of the tumors. MRI plain scan may not be able to identify the true tumor or pseudo-tumor, benign or malignant, but the enhanced scan can help to do differential diagnosis [6].

Nevertheless, about 5% of the tumors still cannot be diagnosed through imaging examination, and in this situation you can do a diagnostic vitrectomy. Through the vitrectomy, a small number of specimens are obtained, so that we can perform the pathologic diagnosis and cytogenetic examination of tumors, to make further clinical diagnosis and classification for suspicious tumors, as well as assess the prognosis of tumors, which is very meaningful [4].

17.4 Treatment of Uveal Melanoma

In terms of the treatment of uveal melanoma, there has been some progress in recent years. However so far, there are still two major controversies in the treatment: one treatment method is eyeball extraction, and another is the eyeball preservation. In fact, there is no way to change the survival status of patients with uveal melanoma, because we still have no way to prevent the metastasis of the tumor. COMS is a very valuable clinical study done many years ago in North America, which is a multicenter, prospective, and randomized clinical study. This study has been going on for more than a decade and has covered more than 3000 cases. The efficacy differences between eyeball enucleation and radiotherapy on uveal melanoma are compared, and the results showed that there was no significant difference in therapeutic efficacy between eyeball enucleation and episcleral plaque radiotherapy for the treatment of medium tumor. That is to say, it was not necessary to remove the eyeball [7]. Another research has been done in Europe in the year 2008, and found that nearly a decade after adopting integrated treatment the patient's 5-year survival rate has not worsened than before; that is, compared with the eye enucleation treatment, the eye-retaining treatment did not increase the rate of metastasis and mortality [8]. It has two levels of meaning: on the one hand integrated treatment did not have a negative impact on the prognosis of uveal melanoma, and on the other hand the survival rate of patients has seen no significant improvement up to now.

As a result, a consensus has been reached now on the ideal integrated treatment of uveal melanoma. For large tumors, eyeball enucleation is the suggested treatment, but for small and medium tumors we should try to retain the eyeball and preserve visual acuity as much as possible. The preferred treatment method is episcleral plaque radiotherapy, followed by the method of the transpupillary thermotherapy (TTT), proton beam radiotherapy, stereotactic radiotherapy, as well as local resection of the tumor.

Episcleral plaque radiotherapy is the preferred method of conservative treatment [9]. There are many types of radioactive particles. No matter what kind of particles you choose, there is little difference in clinical efficacy. The studies from North America and us both have chosen

Fig. 17.2 Domestic episcleral plaque

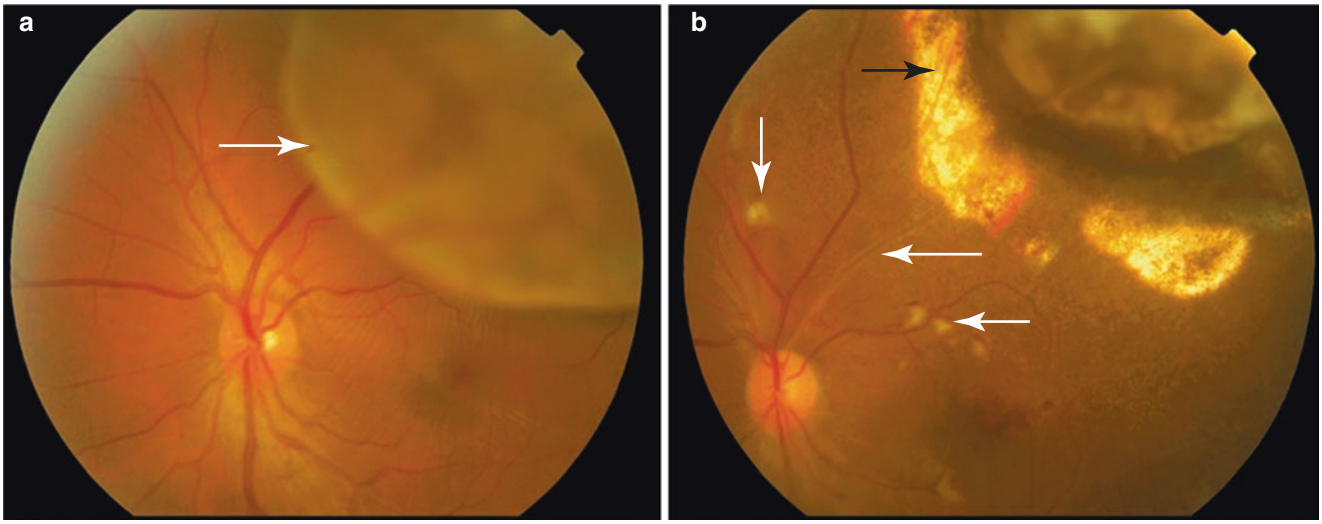

Fig. 17.3 A case of choroidal melanoma treated by episcleral plaque radiotherapy. (**a**) Pretreatment and (**b**) posttreatment

iodine-125 as radioactive source. Figure 17.2 shows a homemade episcleral plaque made by us and the Chinese Academy of Atomic Energy. Iodine-125 is relatively easy to be managed, which is of gamma ray and can be shielded by 1 mm thick metal screen, so the side effects of radiation therapy can be reduced. After a certain dose of exposure, the plaque can be removed. Figure 17.3 shows a clinical case that after episcleral plaque radiotherapy, the melanoma is reduced significantly and the surrounding choroids are also shrunken, indicating that the size of the plaque is appropriate for covering the entire tumor. But regardless of the distance, radiotherapy for a long time is likely to cause radioactive retinopathy. In this case, we can see some cotton wool spot of the posterior pole after 2 years of radiotherapy, which is related to radioactive retinopathy.

Radiotherapy for choroidal melanoma is significantly different from choroidal hemangioma and choroidal metastatic cancer. Hemangioma can be completely shrunken after radiotherapy, while melanoma will become only thinner, but not completely shrunken. As shown in Fig. 17.4, the first reaction after radiotherapy is the reduction of subretinal fluid. The retinal detachment in macular area is observed before radiotherapy, and disappeared after a month of treatment. The reduction and disappearing of subretinal fluid have indicated the effectiveness of radiotherapy. However, in some patients, the subretinal fluid is absorbed after radiotherapy, but macular cystoid edema occurred, as shown in Fig. 17.5, which is a side effect of radiotherapy.

No matter what kind of radiotherapy, radioactive retinopathy can always occur after treatment, and now there are some ways to solve this problem. If the thickness of the tumor is less than 4 mm, TTT treatment alone is enough, and if the thickness is more than 4 mm we can choose the so-called sandwich treatment, which is a combination of TTT and episcleral plaque radiotherapy. We have accumulated some experience in this respect, and a related report is conducted in the year 2011 [10]. The proton beam radiotherapy is another choice, but accelerator is needed. In addition, we can carry out stereotactic radiotherapy. Due to the development of stereotactic radiosurgery, some of the medium-to-large tumors can be treated through stereotactic stereotaxis. We have conducted a long-term cooperation with the Cancer Hospital of Chinese Academy of Medical Sciences. Through stereotactic radiotherapy, a considerable number of patients with medium-to-large tumors were treated successfully, and to some extent the eyeball and life of these patients were saved [11]. Of course, we have started early to do local resection of uveal melanoma. Local resection can be a good way to save the eyeball or even the vision in some patients with certain iris tumors, ciliary body tumors, and choroidal tumors. At the same time, we have done some clinical pathology and molecular pathology research with these resected specimens.

Nevertheless, metastasis is still one of the biggest clinical problems of melanoma that cannot be ignored, and is also an important factor affecting the survival rate. Uveal melanoma is mainly transferred to the liver. After occurrence of liver metastasis, the survival period is generally less than a year [12]. The COMS study found that the proportion of tumor metastases is still relatively high, and the survival rate is relatively low when metastasis occurred, with the annual survival rate less than 19%, and 2-year survival rate less than 10% [13]. So metastasis is the biggest problem of the tumor. In clinical practice, special attention is given on how to screen out patients with a high degree of malignancy. In fact, it is the study of prognostic factors. Traditional prognostic indicators mainly include histopathological features such as

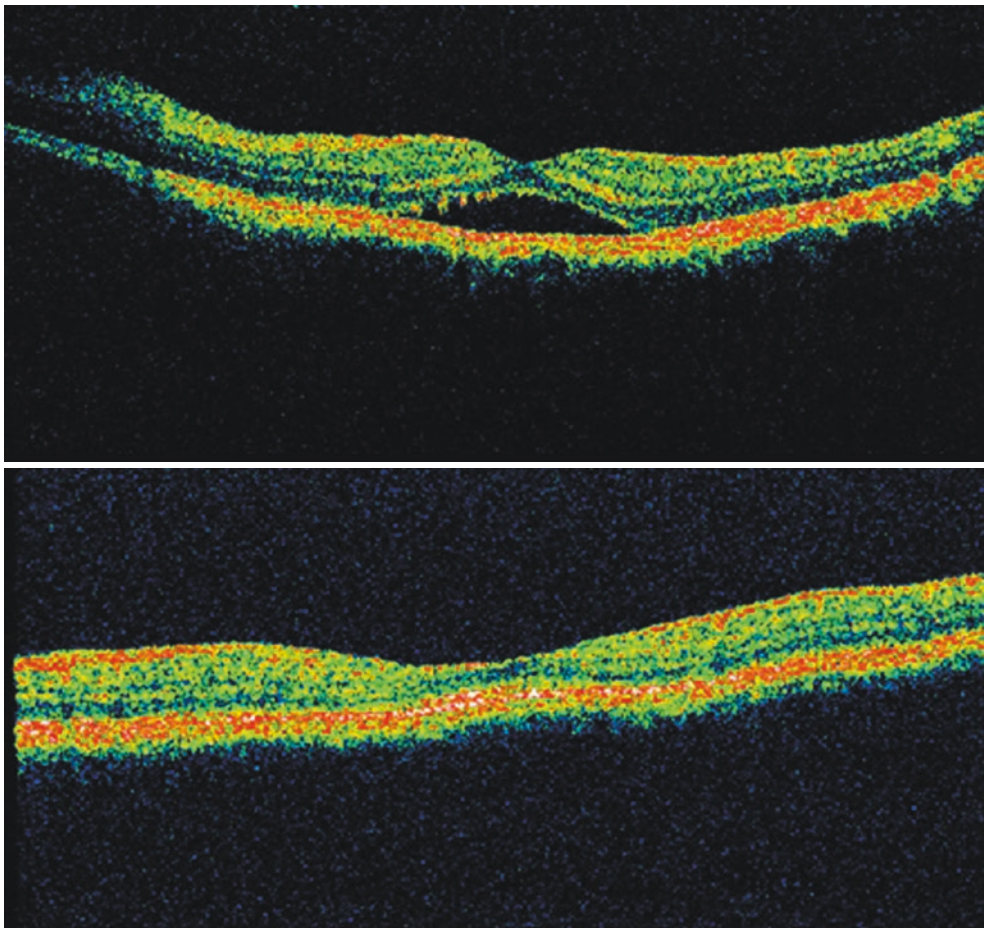

Fig. 17.4 OCT images of a case of choroidal melanoma treated by episcleral plaque radiotherapy. Upper: There was local shallow detachment of neuroepithelial layer before treatment. Lower: The neuroepithelial layer detachment recovered after treatment

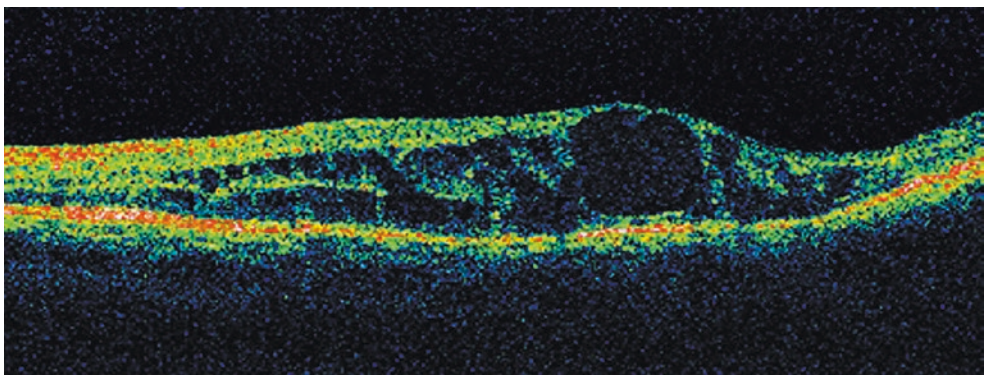

Fig. 17.5 Examination showed cystoid macular edema in a patient with choroidal melanoma after episcleral plaque radiotherapy

cell type, microvascular density, tumor-infiltrating macrophages, and gross anatomical features such as tumor basal diameter, and whether the tumor infiltrates the ciliary body, but its accuracy and specificity have been unable to meet the clinical demands. Some new prognostic indicators have been found nowadays. In terms of cytogenetic characteristics, it has been found that deletion of chromosome 3 is an important predictor of tumor metastasis, as well as an increase of chromosome 8. Therefore, fine-needle aspiration biopsy and diagnostic vitrectomy are very valuable methods for assessing the prognosis of the tumor [14, 15]. In addition, uveal melanoma can also be divided into two types according to the analysis of gene expression profile, type I belonging to low risk of metastasis, with 7-year survival rate of more than 95%, and type II belonging to high risk of metastasis, with 7-year survival rate of only 30% [16]. Compared with the traditional indicators, the indicators of cytogenetics are more accurate and more objective to predict the risk of metastasis, which is very significative for clinical practice [17]. For those patients with better prognosis, excessive psychological burden and unnecessary frequent examinations can be avoided, and for those patients with poor prognosis close

clinical monitoring or consideration of clinical trials with systemic medication is needed.

The future directions of uveal melanoma treatment should mainly focus on the tumor molecular targeted drug therapy, tumor immunotherapy, and antiangiogenesis therapy.

References

1. Egan KM, Seddon JM, Glynn RJ, et al. Epidemiologic aspects of uveal melanoma. Surv Ophthalmol. 1988;32(4):239–51.
2. Singh AD, Damato B, Howard P, et al. Uveal melanoma: genetic aspects. Ophthalmol Clin N Am. 2005;18(1):85–97, viii.
3. Singh AD, Rennie IG, Seregard S, et al. Sunlight exposure and pathogenesis of uveal melanoma. Surv Ophthalmol. 2004; 49(4):419–28.
4. Wei W, Tu Y. Clinical application and minimally invasive prospect of diagnostic vitreous surgery. Chin J Ophthalmol. 2010;46(11):1052–6.
5. Yang WL, Wei WB, Li DJ. Characteristics of choroidal melanoma in contrast-enhanced ultrasonography. Zhonghua Yan Ke Za Zhi. 2013;49(5):428–32.
6. He L, Xian J, Wang Z. MRI diagnosis of uveal melanoma. J Clin Radiol. 2005;24(9):779–81.
7. Diener-West M, Earle JD, Fine SL, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS report no. 18. Arch Ophthalmol. 2001;119(7):969–82.
8. Virgili G, Gatta G, Ciccolallo L, et al. Survival in patients with uveal melanoma in Europe. Arch Ophthalmol. 2008;126(10):1413–8.
9. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. Ophthalmology. 2002;109(12):2197–206.
10. Zhou J, Wei W, Wang G. Preliminary observation on the treatment of choroidal melanoma by application of patch radiation combined with transpupillary thermotherapy. Chin J Ocular Fundus Dis. 2011;27(1):29–32.
11. Xiao JP, Xu G, Miao Y. A preliminary study on stereotactic radiotherapy for choroidal malignant melanoma. Chin J Oncol. 2005;27(4):241–4.
12. Rietschel P, Panageas KS, Hanlon C, et al. Variates of survival in metastatic uveal melanoma. J Clin Oncol. 2005;23(31):8076–80.
13. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. J Clin Oncol. 2004;22(12):2438–44.
14. Prescher G, Bornfeld N, Hirche H, et al. Prognostic implications of monosomy 3 in uveal melanoma. Lancet. 1996;347(9010):1222–5.
15. Sisley K, Rennie IG, Parsons MA, et al. Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis. Genes Chromosomes Cancer. 1997;19(1):22–8.
16. Onken MD, Worley LA, Ehlers JP, et al. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. Cancer Res. 2004;64(20):7205–9.
17. Robertson DM. Cytogenetics in the management of uveal melanoma: are we there yet? Arch Ophthalmol. 2008;126(3):409–10.

Integrative Analysis of Uveal Melanoma

18

Xiaolin Xu and Xiao Zhang

18.1 Introduction

The difficulty of treatment of malignant tumors reflects the complexity of life sciences. The histo- and cytopathological changes from the previous histopathological diagnosis and the macroscopic imaging changes from a variety of imaging diagnosis have provided irreplaceable information for the diagnosis and prognosis evaluation of tumors. In recent years, with the development of molecular biology, the solutions for the difficult problems of oncology have been found out. The essence of tumor metastasis refers to the "invasive property" of cancer cells, which is the result of a series of genetic changes, fundamentally. Under what conditions the gene mutated to form the benign nevus, and under what conditions the gene mutated to form the invasive melanoma? From the view of dialectics, is there a possibility of mutual transformation? The ideal situation is to solve the macroscopic problems such as metastasis of malignant tumor through microscopic approaches, and then come back to the macroscopic level to achieve the prediction of tumor metastasis and the development of new drugs. Under the guidance of integrative medicine, we are looking forward to a promising future.

Uveal melanoma is a special eye disease, and also a lethal intraocular tumor, and represents a systemic disease. It not only seriously affects the patient's visual function, but also is likely to cause death through metastasis. The specificity of this tumor is that it is divided into two categories from the tumorigenesis. In the lucky group of patients, as long as the primary eye tumor is treated properly, the patient's prognosis is good. However, as for what is the proper treatment, the famous uveal melanoma research COMS has given a definite answer. For the less fortunate group of patients, the metastasis of the tumor will happen sooner or later, and about half of the patients died because of tumor metastasis within 15 years of the diagnosis [1, 2]. So far, there is no effective treatment measure for patients who have undergone tumor metastasis. The mechanism of tumor metastasis is still not clear. Thirty-five years ago, eye pathologist Zimmerman has put forward the question whether eyeball enucleation is to prevent or to accelerate the spread of the tumor metastasis [3]. Today, we still cannot answer this question, because we are not clear about the mechanism of tumor metastasis.

With the advancement of medical biology, our understanding of uveal melanoma is progressed gradually. In the past our knowledge has been limited to traditional histopathology, and this is the primary tool for understanding uveal melanoma. Until 20 years ago, we have recognized the change in chromosomes, and even in the last 5 years, owing to the important discoveries in the field of this tumor molecular genetics, we have made considerable progress in the understanding of uveal melanoma. Here we explain the cognitive process of uveal melanoma from four aspects, including histopathological features, chromosome changes, gene expression profile, and molecular signaling pathway abnormality.

18.2 Histopathological Features

In the past, in the absence of molecular biology means, histopathological features are very important to determine the prognosis of uveal melanoma. It is generally recognized that the prognosis of spindle cell tumors is better than that of epithelioid cell tumor (Fig. 18.1), because the former is not prone to metastasis [4]. There are many similar indicators, such as larger basal diameter of the tumor, invasion of the ciliary body (Fig. 18.2), invasion of the scleral catheter (Fig. 18.3), and vasculogenic mimicry. They are actually

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_18

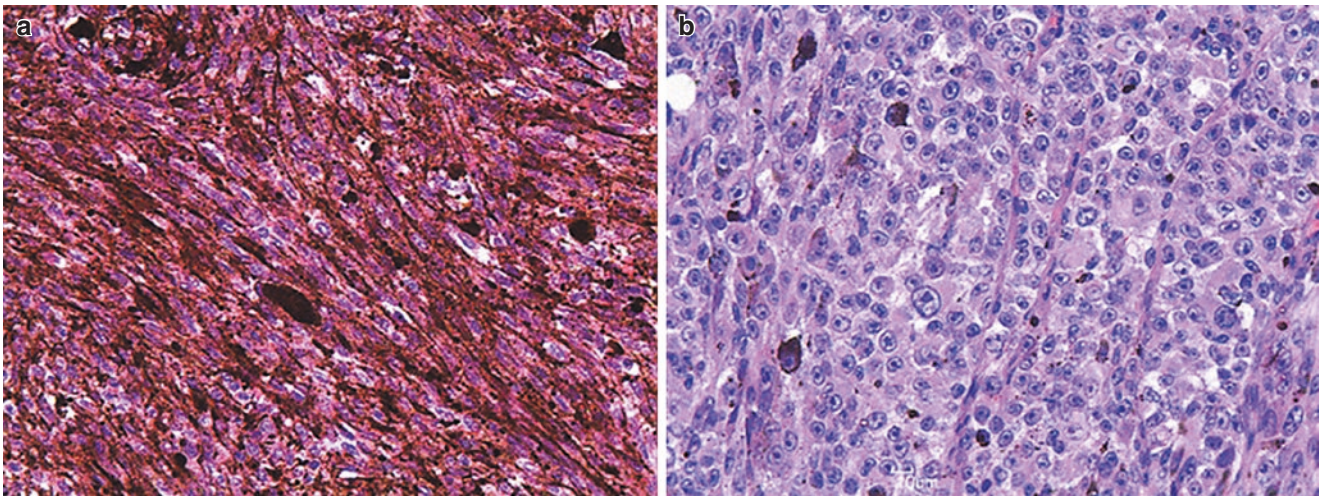

Fig. 18.1 Histopathological types of uveal melanoma. (**a**) Spindle cell type and (**b**) epithelioid cell type

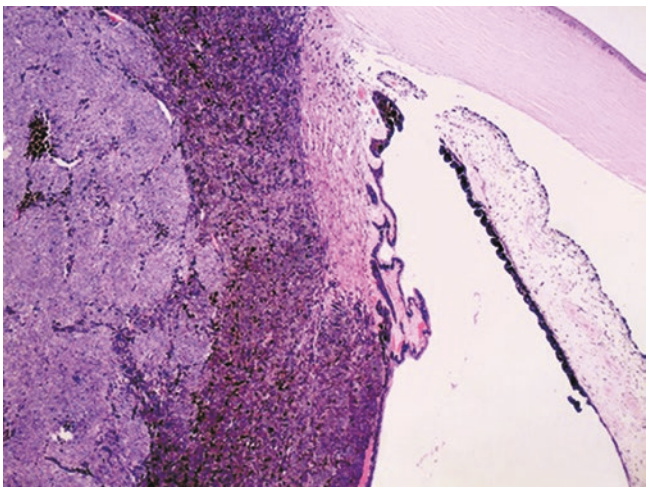

Fig. 18.2 Invasion of ciliary body in uveal melanoma

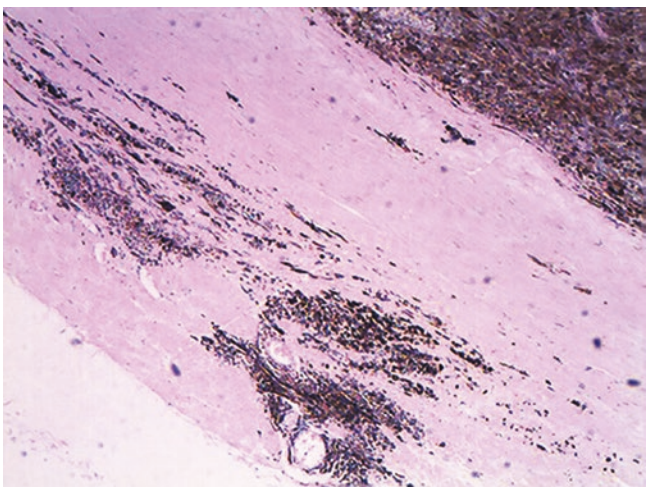

Fig. 18.3 Invasion of scleral canal in uveal melanoma

some characteristics of cell morphological aspects, or indicators of gross anatomy aspects. These indicators are important for assessing the prognosis of uveal melanoma for a long period of time.

18.3 Chromosomal Abnormalities

In 1992, it was reported that there were chromosomal abnormalities in uveal melanoma. These anomalies may involve chromosomes 1, 3, and 8, and the most common is the deletion of chromosome 3 monosomy. In 1996, an article published by "The Lancet" reported that chromosome 3 deletion was closely related to metastasis of uveal melanoma [5]. Until present, the haplotype chromosome 3 has been recognized as a reliable indicator for predicting metastasis of uveal melanoma for many years. There are many methods to detect this indicator, and the most commonly used is fluorescence in situ hybridization (FISH), as well as multiplex ligation-dependent probe amplification (MLPA). In the Western countries, the detection of the haplotype chromosome 3 of uveal melanoma has become a routine test. In 2010, American scholars Harbor et al. found BAP1 gene mutation on haplotype chromosome 3, and this mutation occurred in almost all of the metastatic uveal melanoma. This finding is very important, and is of great significance in elucidating the mechanism of tumor metastasis [6].

18.4 Gene Expression Profile

Harbor et al. divided uveal melanoma patients into two classes including Class 1 and Class 2 through gene expression profile and clustering analysis. Patients in Class 1 have low risk of metastasis, high survival rate, rare haplotype chromosome 3, and less BAP1 gene mutation. But patients in Class 2 are on the contrary. At present, this technique has been transformed into clinical diagnostic reagent [7].

18.5 Molecular Pathway Abnormalities

Molecular pathway abnormalities of uveal melanoma involved RB1, P53, PI3K, MAPK pathway, and so on. Activation of MAPK pathway has been clearly identified in uveal melanoma, but the key gene mutation in this pathway has not been found. In cutaneous melanoma, the activation of the MAPK pathway has a definite cause, such as the BRAF gene mutation or the NRAS gene mutation, which causes MAPK pathway activation. Based on these mutations, there is now corresponding molecular targeted drug, which has achieved significant effect in clinical treatment. In 2008, GNAQ and GNA11 gene mutations were found in uveal melanoma, which encode the G protein in upstream of the MAPK pathway, and the overall mutation rate is 83%. GNA11 mutation occurs more in metastatic melanoma, and through cell function experiments as well as animal experiments it is found that this mutation can promote the metastasis of uveal melanoma [8].

In summary, the main molecular events in uveal melanoma can be summarized as follows: Because of GNAQ and GNA11 gene mutations, melanocytes may undergo abnormal proliferation, or become nevus or melanoma. The key rate-limiting step in the malignant transformation may lie in chromosome 3 and BAP1 genes, while GNAQ and GNA11 gene mutations may be early events in the development process.

On this basis, our research team also tested GNAQ and GNA11 mutations in Chinese patients with uveal melanoma and found that the total mutation rate was 38%, which differs greatly compared with the mutation rate of 83% in the Caucasian patients. We will continue to test all the exons of the GNAQ and GNA11 genes, in order to detect mutations in Chinese-specific pathogenic genes [9].

If haplotype chromosome 3 and gene expression profiles are of great value in the prediction of metastasis of uveal melanoma, then GNAQ, GNA11, as well as BAP1 have unprecedented significance in the design of molecular targeted drugs for the treatment of uveal melanoma metastases. Although it is currently technically difficult to design molecular targeted drugs for both of them, preliminary studies have shown that molecular targeted drugs in downstream of the MAPK pathway have an inhibitory effect on uveal melanoma and some of the drugs have entered the clinical trial stage of uveal melanoma treatment [10].

The existing means for the patients with metastases of uveal melanoma have very limited treatment effect. However, based on current research progress, for the prediction of metastasis, and the development of molecular targeted drugs, we still have a reason to expect a promising future of uveal melanoma treatment.

References

1. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. Ophthalmology. 2002;109(12):2197–206.
2. Diener-West M, Reynolds SM, Agugliaro DJ, et al. Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. J Clin Oncol. 2004;22(12):2438–44.
3. Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells. Br J Ophthalmol. 1978;62(6):420–5.
4. Damato B, Eleuteri A, Taktak AF, et al. Estimating prognosis for survival after treatment of choroidal melanoma. Prog Retin Eye Res. 2011;30(5):285–95.
5. Prescher G, Bornfeld N, Hirche H, et al. Prognostic implications of monosomy 3 in uveal melanoma. Lancet. 1996;347(9010):1222–5.
6. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. Science. 2010;330(6009):1410–3.
7. Onken MD, Worley LA, Ehlers JP, et al. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. Cancer Res. 2004;64(20):7205–9.
8. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. N Engl J Med. 2010;363:2191–9.
9. Xu X, Wei WB, Li B, et al. Oncogenic GNAQ and GNA11 mutations in uveal melanoma in Chinese. PLoS One. 2014;9(10):e109699.
10. Infante JR, Papadopoulos KP, Bendell JC, et al. A phase 1b study of trametinib, an oral mitogen-activated protein kinase kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours. Eur J Cancer. 2013;49:2077–85.

Update on Diagnosis and Treatment of Primary Vitreoretinal Lymphoma

19

Xiao Zhang and Meifen Zhang

19.1 Introduction

Primary vitreoretinal lymphoma (PVRL) is one manifestation of primary central nervous system lymphoma (PCNSL) and typically a systemic disease. It often masquerades as chronic uveitis, especially posterior and pan-uveitis, and is frequently misdiagnosed at first. The golden standard for diagnosis is malignant lymphoid cells from the eye. Cytology and immunohistochemistry could confirm the diagnosis of PVRL. Flow cytometry, gene rearrangement, and intraocular cytokine detection are important auxiliary examinations. New methods using microRNA, gene mutation, and SNP might be helpful in the diagnosis and treatment response monitoring. Treatments of PVRL include systemic and local therapy. Intravitreal methotrexate and ocular radiotherapy are used for PVRL patients without brain involvement. Intravitreal anti-CD20 agent is a relatively new therapy, and seems to be safe and effective.

In 1953, Givner reported a patient with uveitis and died as a result of a malignant lymphoma of the brain [1]. Subsequently, ophthalmologists recognized the disease as intraocular large-cell lymphoma, or reticulum cell sarcoma. Since lymphomas are considered originating from the retina and vitreous body, PVRL is now used, but it is also known as primary intraocular lymphoma (PIOL). PVRL is a rare type of PCNSL, but is the most common lymphoma of the eye [2, 3]. Most patients are older than 50 years old, with median age range of 60s. Approximately 15–25% of patients with PCNSL have or will have ocular involvement. Conversely, 56–90% of patients with PVRL ultimately develop CNS disease [3]. The prognosis of PVRL is poor due to its close relationship with PCNSL.

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19.2 Ocular Features

PVRL usually masquerades as chronic posterior or pan-uveitis, but it is unresponsive to corticosteroids or initially responsive to the therapy [4, 5]. In a retrospective review of 853 patients seen at the National Eye Institute Uveitis Clinic, 21 (2.5%) were diagnosed with neoplastic masquerade syndromes [6]. Common symptoms of PVRL at presentation are decreased visual acuity, blurred vision, and floaters. Most patients have bilateral lesions, but some of them may present symptoms unilaterally. Anterior segment inflammation is not obvious in most PVRL cases. There may be nonspecific manifestations such as different types of keratic precipitates and anterior chamber cells [4, 5, 7].

Vitreous cells and haze are typical signs of PVRL, often striking. As the most common ocular finding, vitreous cells may form clumps, sheets, or strands (Fig. 19.1a). Another typical sign is multifocal creamy infiltrative lesions in the deep retina [4, 5, 7]. These lesions may be located in the subretina, intraretinal, and subretinal pigment epithelial (RPE) regions. They can have distinct borders, as well as feathery borders (Fig. 19.1b). In advanced cases, exudative retinal detachment may be presented (Fig. 19.1c). RPE atrophy with or without subretinal fibrosis was left after treatment (Fig. 19.1d).

19.3 Diagnose Methods

19.3.1 Ocular Biopsy

The golden standard for diagnosis of PVRL is detection of malignant lymphoid cells in the eye, including the retina, vitreous body, and optic nerve. Surgical procedures include diagnostic vitrectomy, puncture of anterior chamber, chorioretinal biopsy, and diagnostic enucleation [4, 8]. Currently, diagnostic vitrectomy is the most common method, and detection of lymphoma cells in vitreous sample is essential. Mudhar and Sheard revealed that specimens from pars plana

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_19

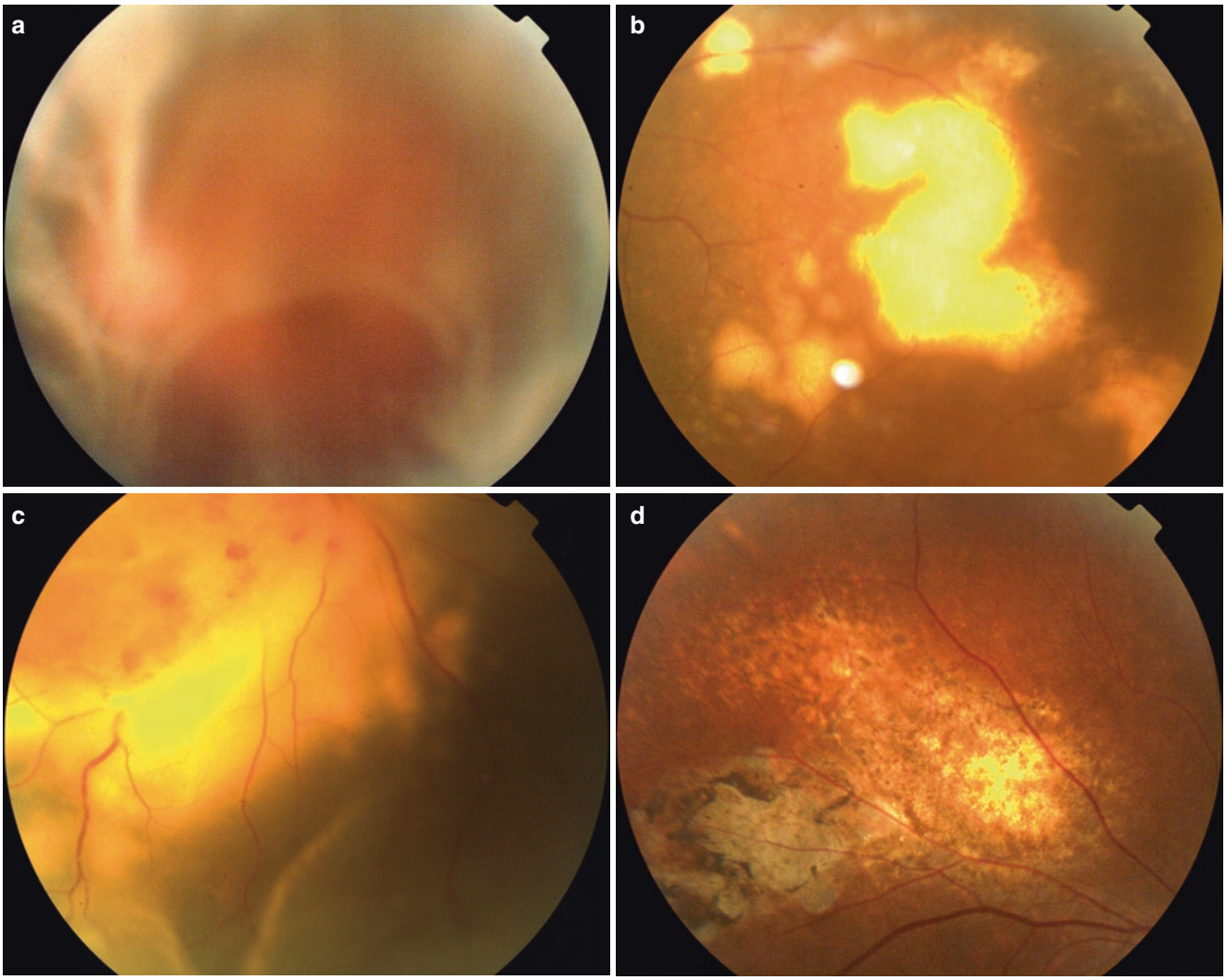

Fig. 19.1 Ocular features of PVRL. (**a**) Vitreous haze. (**b**) Multifocal creamy infiltrative lesions in the deep retina. (**c**) Exudative retinal detachment with subretinal lesions. (**d**) RPE atrophy after treatment

vitrectomy had an average cellularity of 31×, which is greater than specimens from core vitreous biopsy, so they speculated that the cells were more concentrated in the cortical vitreous body [9]. We generally use standard three-port pars plana vitrectomy to collect 1–2 mL undiluted vitreous biopsy without infusion for cytological examination. After that, open the infusion and collect some dilute vitreous sample for other examinations. Some authors suggested low cut rate and gentle aspiration during the vitrectomy [10, 11].

Because of the small amount of sample and cell fragility, diagnosis of PVRL is usually difficult to confirm [8]. It is reported that >40% of vitreous samples may remain without diagnosis after vitrectomy [12]. Promptly and properly handling the vitreous sample is very important, because the lymphoma cells are too fragile to survive. With the development of surgical techniques, cell preservation in culture medium, and cytological examination techniques, more PVRL cases were diagnosed in recent years. Ranty and colleagues showed a protocol of optimized management of vitreous samples in their study [13]. They suggested to preserve the vitreous sample in culture medium containing RPMI-1640, decomplemented fetal bovine serum, and gentamicin, and perform the whole procedure at 4 °C. Cytological examination with May–Grünwald–Giemsa staining and immunocytochemistry were performed on cytospins. With special focus on pre-analytical steps, diagnostic performance was improved [13].

The other reason for low diagnostic rate is corticosteroid treatment before diagnostic vitrectomy. Almost all of the experts agreed that negative results are common in the first diagnostic vitrectomy biopsy with patients receiving corticosteroids or any immunosuppressive treatment [14]. Repeated operations for cytological examinations are needed when PVRL is highly suspected [10, 14].

19.3.2 Cytology and Immunohistochemistry

According to WHO lymphoma classification, PVRL in most cases is subtyped as diffuse large B-cell lymphoma (DLBCL). Giemsa or Diff-Quick staining is better to detect the characteristics of malignant B cells [7]. Lymphoma cells are characterized by minimal basophilic cytoplasm and prominent nucleoli (Fig. 19.2) [15]. Necrosis and apoptosis, as well as reactive inflammatory cells, are frequently observed in these tumor cells, so the diagnosis is more difficult [7, 15].

Monoclonality immunophenotype supports the cytological diagnosis of lymphoma. Immunohistochemically, B cells from PVRL are characterized by CD79a+, CD19+, CD20+, PAX-5+, BCL2+, IRF4/MUM1+, etc., as well as monotypical for IgM [15]. Ki-67 staining is usually very high in PVRL patients, showing the rapid growth of tumor cells.

19.3.3 Flow Cytometry

Flow cytometry is a useful technique to obtain immunophenotyping, and works similar to immunocytological techniques. Flow cytometry allows the simultaneous application of multiple monoclonal antibodies to a small number of suspected lymphoma cells, thus allowing the use of larger detection panel [16]. But the problem of this method is contamination by heterogeneous population of B and T cells, and may cause difficulty to interpret the results [14]. Another problem with this method is background noise, which may mask signals from lymphoma cells when there are few interested cells, as is often the case in PVRL [5]. Meanwhile, flow cytometric immunophenotyping usually requires relatively larger amount of sample, but ocular specimens are often limited. In summary, the application of immunophenotyping analysis for PVRL detection using flow cytometry could be restricted.

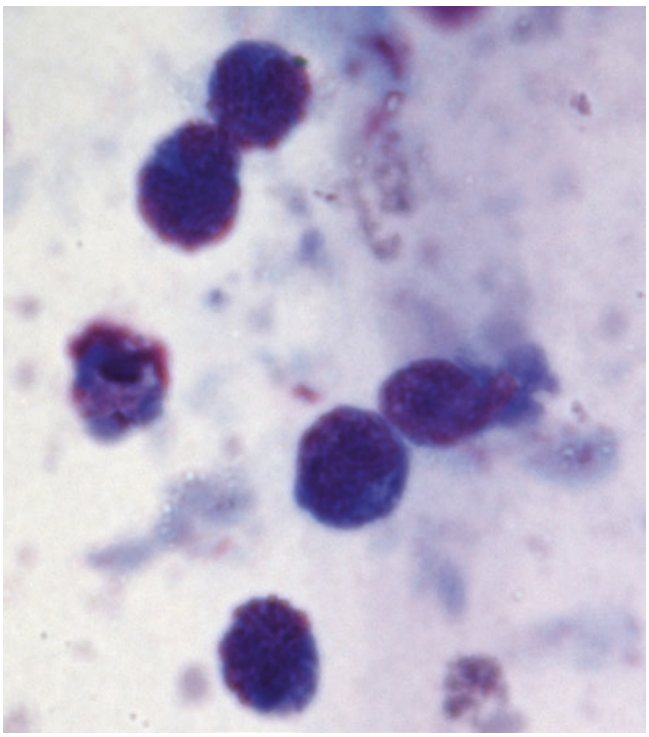

Fig. 19.2 Cytology of PVRL cells in the vitreous

19.3.4 Molecular Analyses

Microdissection and monoclonal rearrangement are used in the molecular analysis for PVRL. Relative pure atypical lymphoid cell population (PVRL cells) from cytological or histopathological slides is selected using microdissection, and DNA and RNA are extracted and analyzed to characterize the cells [14]. Monoclonal rearrangements such as immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) genes can be detected. Chan reported a series of 57 PVRL patients; IgH rearrangements were demonstrated in all 50 tested cases [17]. Wang and colleagues have observed a series of 208 cases with masquerade syndrome; both the sensitivity and specificity of molecular markers in diagnosis of PVRL are higher than 95% [18]. Although gene rearrangement has high sensitivity, specificity, predictive value, and efficiency for the diagnosis of PVRL, IgH gene rearrangements are not indication of malignant lesions, and should be considered as adjuncts to improve diagnosis [5].

19.3.5 Intraocular Cytokine

High vitreous IL-10 level was first detected in three B-cell PVRL patients in 1995 [19]. Since then more ocular fluid samples of PVRL patients were tested to confirm the elevation of IL-10 [18, 20, 21]. In a series of 51 lymphoma patients and 108 uveitis patients, a cutoff of 50 pg/mL IL-10 in aqueous humor had a sensitivity and specificity of 0.89 and 0.93, respectively, for lymphoma. A cutoff value of 400 pg/mL IL-10 in the vitreous was associated with a specificity and sensitivity of 0.99 and 0.80, respectively [20]. The mean level of IL-6 and IL-10 in vitreous samples of uveitis patients was different from PVRL patients, but overlapping existed in some cases [18, 21]. Combination of the IL-10/IL-6 and IL-10/IFNγ ratios can be used to identify PVRL from uveitis samples [21]. Besides IL-10, levels of various immune mediators in the vitreous elevated, such as BCA-1, bFGF, Fas ligand, and RANTES, indicating the possibility that these factors are involved in the pathophysiology of vitreoretinal B-cell lymphoma [22].

Ecker and colleagues discovered that the concentration of different cytokines in the vitreous and aqueous humor was

different, but cytokine ratio was constant [23]. Fisson et al. also analyzed cytokines in the aqueous humor and vitreous, and reached the same conclusion [21]. The result is quite important because aqueous humor is much easier and safer to obtain, and multiple samples can be acquired. Measurement of IL-10 in the aqueous humor can be used as screening test to determine whether vitreous biopsy is indicated [24], as well as indicators for therapeutic effects and PVRL recurrence [25].

19.3.6 Updates on Probable Diagnostic and Estimated Methods

Tuo and Chan proposed that micro-ribonucleic acid (microRNA) in ocular fluid could be used as a novel marker for the diagnosis of PVRL. Quantification of ocular microRNA-155 might be helpful in the differential diagnosis of primary vitreoretinal B-cell lymphoma and uveitis [26]. However, for the diagnosis of PVRL, vitreous microRNA-155 level had no advantage over ratio of vitreous IL-10 and IL-6 levels.

The same MyD-88 L265P mutation has been shown to occur in about 15% of cases of systemic diffuse large B-cell lymphoma. Pulido and colleagues found that MYD-88 L265P constitutive activation mutations were present in some cases of diffuse large B-cell PVRL [27]. Bonzheim and colleagues identified MYD88 mutations in 20 of 29 confirmed PVRL cases. Detection of MYD88 mutations has improved the diagnosis rate of vitreoretinal B-cell lymphoma. Detection of MYD88L265P will enable more timely treatment and might be useful in monitoring treatment response, and may improve the prognosis of PVRL/PCNSL patients ultimately [28].

As mentioned before, high levels of IL-10 are related to rapid progression of vitreoretinal B-cell lymphoma, as well as PCNS of B-cell origin. Ramkumar and colleagues found IL-10 (-1082) G→A SNP with the GA genotype to be associated with PVRL and PCNSL [29]. It suggested that the IL-10 (-1082) A allele was a risk factor for higher IL-10 levels in PVRL and PCNSL [29].

19.4 Treatment

In 2011, the International Primary Central Nervous System Lymphoma Collaborative Group Symposium recommended the following guidelines of PVRL treatment [3]:

1. For patients without CNS or systemic involvement:
   If only one eye is involved, use local therapy with intravitreal methotrexate, intravitreal rituximab, or 30–35 Gy of external beam radiotherapy (EBRT).
   If both eyes are involved, there is still a preference toward local therapy, but systemic chemotherapy has been suggested in addition to intravitreal medications for bilateral cases.
2. For patients with CNS involvement:
   Systemic treatment is recommended, including chemotherapy in conjunction with local therapy, and whole-brain radiotherapy in conjunction with ocular radiotherapy.

19.4.1 Systemic Therapy

High-dose methotrexate is the most commonly used intravenous chemotherapy, and the doses should reach at least 3 g/m^2 in order to penetrate the blood–brain barrier and yield cytotoxic levels in the cerebrospinal fluid. In order to improve responses, other chemotherapeutic agents such as cytarabine are added [30]. High-dose methotrexate is reported to get a response rate of up to 72% when used alone and 94–100% in combination with other chemotherapeutic agents [5, 31].

Localized brain radiotherapy is usually used as first-line treatment of PCNSL [5]. Whole-brain radiotherapy (WBRT), high-dose methotrexate, and combined treatments make patients face greater risk of neurotoxicity. In patients with residual disease or disease progression, it is suggested to use localized brain radiotherapy with a total dose of 40–45 Gy with a 1.8–2.0 Gy dose per fraction [31].

In cases of refractory or relapsed PCNSL, high-dose chemotherapy combined with autologous stem-cell transplantation (HDC-ASCT) can be considered, and may be an efficient treatment [3].

19.4.2 Local Therapies

Local therapies include ocular radiotherapy and intravitreal chemotherapy. Up to now, there has been no randomized control study to compare the outcomes of these treatments, and no final conclusion that whether intravitreal chemotherapy or ocular radiation should be chosen as first-line therapy.

Intravitreal methotrexate was shown to be efficacious, and a dose of 0.4 mg methotrexate in 0.1 mL is recommended. The frequency of injections varied among different reports, ranging from twice a week to monthly during inductive therapy [32, 33]. The half-life of methotrexate in vitreous is approximately 5 days, so one injection probably has effect for approximately 3–4 weeks [34]. The primary goal of treating PVRL with intravitreal methotrexate is to reduce complications of intraocular lesions, as well as improve vision [8].

A common and characteristic side effect of intravitreal methotrexate is corneal epitheliopathy, which subsided when the injection interval increased [5, 32, 35]. It is reported that

paracentesis before the injection and oral folic acid supplements could minimize drug toxicity and reduce corneal epitheliopathy [35].

Ocular radiotherapy is used to control PVRL disease, maintain vision, and prevent CNS involvement. Radiotherapy alone could achieve high local control rates and improved visual acuity, but could not prevent lymphoma relapse [36, 37]. Complications of ocular radiotherapy include dry eye, cataract formation, radiation retinopathy, and local recurrence. With proper techniques, retinopathy and recurrence could be very low [8, 37].

19.4.3 Updates on PVRL Treatment

In order to reduce the number of methotrexate injections, a sustained-release device with methotrexate has been tested. It is a kind of biodegradable microneedle implant, releasing MTX for a period of more than 1 month, and no toxicity was detected in rabbit test [38].

Rituximab is a first-generation chimeric murine mAb against the CD20 antigen. There have been significant improvements in treatment outcomes for different kind of systemic non-Hodgkin's lymphomas after clinical use of rituximab [39]. Intravitreal rituximab at a dose of 1 mg appeared to be safe in rabbit eyes, and causes no side effects in eyes of five PVRL patients, resulting in reduction of tumor occurrence and growth [40, 41].

From limited reports of intravitreal rituximab for the treatment of PVRL in the literature, this method appears to be safe and effective in a majority of PVRL. Thus the number of intraocular MTX injections can be reduced to minimize the toxicity [39, 42].

Ublituximab is a promising glycoengineered anti-hCD20 mAb with a high affinity for FccRIIIa (CD16) receptors. Ben Abdelwahed and colleagues have found that single doses of intravitreal ublituximab had significant antitumor effect, and the effect was more obvious than the same dose of rituximab [43].

Th17 cell has been proved to participate in the onset of multiple autoimmune diseases. Galand and colleagues demonstrated that Th17-related cytokines may counteract tumor progression via IL-21 production, and Th17 cells as well as their related cytokines are hopefully to become an important adjuvant therapy for PVRL [44].

19.5 Conclusion

Primary vitreoretinal lymphoma is related to central nervous system disease and often masquerades as chronic posterior uveitis. Because it is frequently misdiagnosed at first presentation and the prognosis is poor, differential diagnosis is very important. Golden standard for the diagnosis of PVRL is detection of malignant lymphoid cells inside the eye. Diagnostic vitrectomy is the most common procedure to obtain ocular sample, and it is critical to process the vitreous specimen promptly and properly. A protocol for diagnosis of PVRL was built in our hospital in recent years. Seeing a patient older than 40, with bilateral uveitis of vitreous opacity or yellow subretinal lesions, we should appropriately suspect the diagnosis of PVRL. Enhanced MRI of the head is performed first. If the result of MRI is positive, lumbar puncture is done and cerebrospinal fluid is analyzed by hematologist and neurologists. Sometimes, we work with neurosurgeon to decide whether brain biopsy is needed. If the result of MRI is negative, paracentesis is performed and IL-10/IL-6 in the aqueous humor is measured to determine whether diagnostic vitrectomy is indicated. Cytology and immunohistochemistry examination of undiluted vitreous are done to confirm the diagnosis of PVRL. Gene rearrangement of diluted vitreous is an important auxiliary examination. Flow cytometry and intraocular cytokine detection are used when necessary.

Treatments of PVRL include systemic and local therapy. Systemic chemotherapy is recommended when CNS is involved. Intravitreal methotrexate and/or ocular radiotherapy are used for PVRL patients without brain involvement. Biodegradable microneedle implant loaded with methotrexate may reduce the number of methotrexate injections. Intravitreal anti-CD20 agent is a relatively new therapy, and seems safe and effective.

In summary, PVRL is a rare disease; as an ophthalmologist, we should appropriately consider the differential diagnosis of PVRL, obtain adequate sample for pathological evaluation, work closely with pathologists to clarify the diagnosis, and with hematologists and neurologists to treat and follow up the patients properly.

References

1. Givner I. Malignant lymphoma with ocular involvement: clinicopathologic report. Bull N Y Acad Med. 1954;30(9):721–2.
2. Chan CC, Fisson S, Bodaghi B. The future of primary intraocular lymphoma (retinal lymphoma). Ocul Immunol Inflamm. 2009;17(6):375–9.
3. Chan CC, Rubenstein JL, Coupland SE, Davis JL, Harbour JW, Johnston PB, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16(11):1589–99.
4. Chan CC, Sen HN. Current concepts in diagnosing and managing primary vitreoretinal (intraocular) lymphoma. Discov Med. 2013;15(81):93–100.
5. Sagoo MS, Mehta H, Swampillai AJ, Cohen VM, Amin SZ, Plowman PN, et al. Primary intraocular lymphoma. Surv Ophthalmol. 2014;59(5):503–16.

6. Grange LK, Kouchouk A, Dalal MD, Vitale S, Nussenblatt RB, Chan CC, et al. Neoplastic masquerade syndromes in patients with uveitis. Am J Ophthalmol. 2014;157(3):526–31.
7. Faia LJ, Chan CC. Primary intraocular lymphoma. Arch Pathol Lab Med. 2009;133(8):1228–32.
8. Rajagopal R, Harbour JW. Diagnostic testing and treatment choices in primary vitreoretinal lymphoma. Retina. 2011;31(3):435–40.
9. Mudhar HS, Sheard R. Diagnostic cellular yield is superior with full pars plana vitrectomy compared with core vitreous biopsy. Eye (Lond). 2013;27(1):50–5.
10. Levasseur SD, Wittenberg LA, White VA. Vitreoretinal lymphoma: a 20-year review of incidence, clinical and cytologic features, treatment, and outcomes. JAMA Ophthalmol. 2013;131(1):50–5.
11. Kinoshita Y, Takasu K, Kobayashi TK, Yuri T, Tsubura A, Shikata N. Diagnosis of intraocular lesions using vitreous humor and intraocular perfusion fluid cytology: experience with 83 cases. Diagn Cytopathol. 2015;43(5):353–9.
12. Coupland SE, Bechrakis NE, Anastassiou G, Foerster AM, Heiligenhaus A, Pleyer U, et al. Evaluation of vitrectomy specimens and chorioretinal biopsies in the diagnosis of primary intraocular lymphoma in patients with Masquerade syndrome. Graefes Arch Clin Exp Ophthalmol. 2003;241(10):860–70.
13. Ranty ML, Laurent C, Aziza J, Mahieu L, Olle P, Quintyn JC, et al. Improving the cytological diagnosis of intraocular lymphoma from vitreous fluid. Histopathology. 2015;67(1):48–61.
14. Sen HN, Bodaghi B, Hoang PL, Nussenblatt R. Primary intraocular lymphoma: diagnosis and differential diagnosis. Ocul Immunol Inflamm. 2009;17(3):133–41.
15. Coupland SE. Molecular pathology of lymphoma. Eye (Lond). 2013;27(2):180–9.
16. Zaldivar RA, Martin DF, Holden JT, Grossniklaus HE. Primary intraocular lymphoma: clinical, cytologic, and flow cytometric analysis. Ophthalmology. 2004;111(9):1762–7.
17. Chan CC. Molecular pathology of primary intraocular lymphoma. Trans Am Ophthalmol Soc. 2003;101:275–92.
18. Wang Y, Shen D, Wang VM, Sen HN, Chan CC. Molecular biomarkers for the diagnosis of primary vitreoretinal lymphoma. Int J Mol Sci. 2011;12(9):5684–97.
19. Chan CC, Whitcup SM, Solomon D, Nussenblatt RB. Interleukin-10 in the vitreous of primary intraocular lymphoma. Am J Ophthalmol. 1995;120(5):671–3.
20. Kimura K, Usui Y, Goto H, Japanese Intraocular Lymphoma Study Group. Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. Jpn J Ophthalmol. 2012;56(4):383–9.
21. Fisson S, Ouakrim H, Touitou V, Baudet S, Ben Abdelwahed R, Donnou S, et al. Cytokine profile in human eyes: contribution of a new cytokine combination for differential diagnosis between intraocular lymphoma or uveitis. PLoS One. 2013;8(2):e52385.
22. Usui Y, Wakabayashi Y, Okunuki Y, Kimura K, Tajima K, Matsuda R, et al. Immune mediators in vitreous fluids from patients with vitreoretinal B-cell lymphoma. Invest Ophthalmol Vis Sci. 2012;53(9):5395–402.
23. Ecker S, Hines JC, Pfahler SM, Glaser BM. Aqueous cytokine and growth factor levels do not reliably reflect those levels found in the vitreous. Mol Vis. 2011;17:2856–63.
24. Cassoux N, Giron A, Bodaghi B, Tran TH, Baudet S, Davy F, et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. Invest Ophthalmol Vis Sci. 2007;48(7):3253–9.
25. Saleh M, Nikolitch K, Bourcier T, Speeg C, Gaucher D. Repeated IL-10 measurement in aqueous humor and OCT imaging are valuable tools to monitor intraocular lymphoma treated with intravitreal injections of methotrexate. Graefes Arch Clin Exp Ophthalmol. 2012;250(5):761–4.
26. Tuo J, Shen D, Yang HH, Chan CC. Distinct microRNA-155 expression in the vitreous of patients with primary vitreoretinal lymphoma and uveitis. Am J Ophthalmol. 2014;157(3):728–34.
27. Pulido JS, Salomao DR, Frederick LA, Viswanatha DS. MyD-88 L265P mutations are present in some cases of vitreoretinal lymphoma. Retina. 2015;35(4):624–7.
28. Bonzheim I, Giese S, Deuter C, Süsskind D, Zierhut M, Waizel M, et al. High frequency of MYD88 mutations in vitreoretinal B-cell lymphoma: a valuable tool to improve diagnostic yield of vitreous aspirates. Blood. 2015;126(1):76–9.
29. Ramkumar HL, Shen de F, Tuo J, Braziel RM, Coupland SE, Smith JR, et al. IL-10-1082 SNP and IL-10 in primary CNS and vitreoretinal lymphomas. Graefes Arch Clin Exp Ophthalmol. 2012;250(10):1541–8.
30. Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R, et al., European Association for Neuro-Oncology Task Force on Primary CNS Lymphoma. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol. 2015;16(7):e322–32.
31. Bessell EM, Hoang-Xuan K, Ferreri AJ, Reni M. Primary central nervous system lymphoma: biological aspects and controversies in management. Eur J Cancer. 2007;43(7):1141–52.
32. Frenkel S, Hendler K, Siegal T, Shalom E, Pe'er J. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol. 2008;92(3):383–8.
33. STuraka K, Bryan JS, De Souza S, Gordon AJ, Kwong HM Jr, Ziemianski MC, et al. Vitreoretinal lymphoma: changing trends in diagnosis and local treatment modalities at a single institution. Clin Lymphoma Myeloma Leuk. 2012;12(6):412–7.
34. Chu LC, Eberhart CG, Grossman SA, Herman JG. Epigenetic silencing of multiple genes in primary CNS lymphoma. Int J Cancer. 2006;119(10):2487–91.
35. Gorovoy I, Prechanond T, Abia M, Afshar AR, Stewart JM. Toxic corneal epitheliopathy after intravitreal methotrexate and its treatment with oral folic acid. Cornea. 2013;32(8):1171–3.
36. Isobe K, Ejima Y, Tokumaru S, Shikama N, Suzuki G, Takemoto M, et al. Treatment of primary intraocular lymphoma with radiation therapy: a multi-institutional survey in Japan. Leuk Lymphoma. 2006;47(9):1800–5.
37. Mikami R, Nakayama H, Goto H, Kimura K, Usui Y, Nogi S, et al. Preliminary results of radiotherapy for primary intraocular non-Hodgkin lymphoma. Leuk Lymphoma. 2013;54(10):2181–4.
38. Manna S, Banerjee RK, Augsburger JJ, Al-Rjoub MF, Donnell A, Correa ZM. Biodegradable chitosan and polylactic acid-based intraocular micro-implant for sustained release of methotrexate into vitreous: analysis of pharmacokinetics and toxicity in rabbit eyes. Graefes Arch Clin Exp Ophthalmol. 2015;253(8):1297–305.
39. Siegal T. Primary central nervous system lymphoma: current state of anti-CD20 therapy and appraisal of reported response criteria. J Clin Neurosci. 2014;21(5):709–15.
40. Kitzmann AS, Pulido JS, Mohney BG, Baratz KH, Grube T, Marler RJ, et al. Intraocular use of rituximab. Eye (Lond). 2007;21(12):1524–7.
41. Mineo JF, Scheffer A, Karkoutly C, Nouvel L, Kerdraon O, Trauet J, et al. Using human CD20-transfected murine lymphomatous B cells to evaluate the efficacy of intravitreal and intracerebral rituximab injections in mice. Invest Ophthalmol Vis Sci. 2008;49(11):4738–45.
42. Larkin KL, Saboo US, Comer GM, Forooghian F, Mackensen F, Merrill P, et al. Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. Br J Ophthalmol. 2014;98(1):99–103.
43. Ben Abdelwahed R, Donnou S, Ouakrim H, Crozet L, Cosette J, Jacquet A, et al. Preclinical study of Ublituximab, a Glycoengineered anti-human CD20 antibody, in murine models of primary cerebral and intraocular B-cell lymphomas. Invest Ophthalmol Vis Sci. 2013;54(5):3657–65.
44. Galand C, Donnou S, Crozet L, Brunet S, Touitou V, Ouakrim H, et al. Th17 cells are involved in the local control of tumor progression in primary intraocular lymphoma. PLoS One. 2011;6(9):e24622.

Part V

Cardiovascular and Cerebrovascular Diseases and Eye Disease

Correlation Between Coronary Heart Disease and the Retinal Arteriovenous Ratio

20

Jun Wang and Qi Zhou

20.1 Introduction

Cardiovascular disease, especially the coronary heart disease, currently has the highest mortality. The main risk factors of the disease are high blood pressure, high blood lipid, age, family history, smoking, diabetes, obesity, etc. The retinal vessels are the only vessels in human body that are non-invasively observable in vivo that belong to small vessels and are a part of the microcirculation. Traditional ophthalmology only relies on the clinical staging of hypertensive or atherosclerotic retinopathy as clinical evidence for diagnosis and treatment. However from the cardio-cerebrovascular department's perspective, evidences from retinal blood vessels are only references for early diagnose and judgment. If confined by the vertical thinking as practiced previously in isolated sub-disciplines, we will find that there are many questions unanswered; some of the macro questions are the following: Among all the risk factors in coronary heart disease, which factors are related with retinal vascular changes? What is the fundamental pathology of the various retinal vascular changes, respectively? If we view the research process of retinal vessel and cardio-cerebrovascular disease with the idea of integrative medicine in mind, we will find that it follows the philosophy of separation and integration, which means that they separate and integrate when the time comes and in a cycled way. In the beginning, due to the common histologic origin and the development of ophthalmoscope, rough retinal vascular evaluation became a window for specialists to evaluate the state of cardiovascular and cerebrovascular disease. Thanks to the development of bioengineering technology, the evaluation for retinal vascular changes became less invasive and more accurate. At the same time, basic experiments not only showed that the pathology behind different retinal vascular changes with different locations and patterns was different, but also that the cellular immune basis and physiologic effects of retinal artery and venous remodeling were different. Through combining the newest idea from the above disciplines, the population-based study had proved the correlation between different types of retinal microvascular changes and cardio-cerebrovascular diseases. This spurred researchers to hypothesize that it may be possible to predict hypertension or coronary heart disease based on changes in retinal microvessels. The concept of integrative medicine will help the complex relationship between retinal vascular changes and cardio-cerebrovascular diseases be researched in a comprehensive, three-dimensional, and multi-perspective way. The future development and combination of biomedical engineering, basic experiments, and epidemiological studies will make the individualized prevention and treatment possible.

20.2 Retinal Vascular Diameter Changes and Coronary Heart Disease from an Integrative Medicine View

Risks factors of coronary heart disease include high blood pressure, high blood lipid, age, family history, smoking, diabetes, obesity, etc., in which hypertension is the main risk factor. These risk factors not only cause coronary artery diseases, but also alter the morphologic pattern of retinal blood vessels, which will lead to a change in diameter of retinal vessels.

In the nineteenth century, Gunn first discovered the damage high intraocular pressure had on the retinal artery system and that retina was the only window available to directly observe the morphologic changes of small vessel. Retinal vessels are important for assessing the systemic microvascular function; changes in diameter may indicate structural damage or altered function, which may be a clue for cardiovascular disease. More and more evidences show that signs of retinal vessels provide a useful pathway that helps to

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_20

determine changes in systemic vascular system and provides references for early diagnosis and judgment of the disease.

The pathophysiological mechanism of retinal vascular diameter changes is not clear, and it is more likely to be related to multiple factors like age, chronic hypertension, atherosclerosis, inflammation, vascular wall dysfunction, and other vascular factors. Morphological changes take place when the blood vessels are stimulated by various stimuli, and this structural and functional change will lead to the so-called vascular remodeling. Its pathology basis is the increase of cell number, hypertrophy of cells, thickening of fibers, and increase of matrix volume. These pathological changes differ in vessels with different diameters. In general, the arteriolar wall will show a narrowing of the inner diameter and an inward hypertrophic remodeling. Because retinal vessel lacks adrenergic vasoconstrictor nerve to control vascular tension, it is hypothesized that the retinal blood flow depends on the myogenic modulation of arterial tension or other mechanisms, such as endothelial function and metabolic self-regulation [1]. Among them, nitric oxide (NO)-dependent endothelial dysfunction may be involved in the pathological process of retinal artery stenosis [1]. The widening of retinal venous diameter indicates that ischemic changes are associated with elevated level of systemic inflammatory factors and endothelial dysfunction. Venous dilation influences the concentrations of a series of inflammatory factors, including the C-reactive protein and interleukin-6 [2]. In addition, the dilation of veins also contributes to an increase of NO production and a release of inflammatory factors from the activated vascular endothelial cells [3]. Therefore, we speculate that the change in internal diameter of small vessels is an indicator for pathological status of hypertension, and is important for the prognosis and outcome of the disease.

Currently, there are several large epidemiology studies on the relationship between retinal vascular diameter and coronary heart disease: the Cardiovascular Health Study (CHS), the Atherosclerosis Risks in Communities Study (ARIC), the Multi-Ethnic Study of Atherosclerosis (MESA), the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), the Beaver Dam Eye Study (BDES), the Wisconsin Epidemiology Study (WES), the Pittsburgh epidemiology of Diabetes Complications (EDC), the Australia Blue Mountains eye study (BMES), the Singapore Malay Eye study (SiMES), and the Holland Rotterdam study (RS).

20.3 Hypertensive Retinopathy

Hypertension is one of the most important risk factors of coronary heart disease. It is also the leading cause of retinal vein occlusion. Hypertensive retinopathy is the change of microcirculation of the retina caused by the elevated blood pressure [4]. There is no uniform standard for hypertensive retinopathy staging. The widely accepted staging system is the Keith–Wagener–Barker (KWB) Grade [5] (Table 20.1). Keith and colleagues first proposed this staging system in a study in 1939. It is a classic classification of hypertensive retinopathy. Yet the early hypertensive retinopathy changes such as vascular attenuation in Grade I of this classification are sometimes difficult to define clinically. Thus, it is modified and simplified in recent years by some researchers; among them, the staging system published by Tien Won et al. in N Engl J is more representative and has won a wide acceptance (Table 20.2). Compared with the Keith–Wagener–Barker (KWB) Grade, the stages 1 and 2 of this classification are better differentiated and have a higher clinical value.

Table 20.1 Keith–Wagener–Barker (KWB) hypertensive retinopathy classification

Grade I	Mild arteriolar narrowing
Grade II	Arteriolar narrowing and definite focal coarctation and arteriovenous crossings
Grade III	Grade I, II + retinal hemorrhages, microaneurysm, exudates, and cotton wool spots
Grade IV	The above changes with papilledema and macular edema

Table 20.2 Hypertensive retinopathy classification by Tien Wong et al.

None	No detectable signs
Mild	One or more of the following arteriolar signs: generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, arteriolar wall opacity (copper wiring or silver wiring)
Moderate	One or more of the following arteriolar signs: hemorrhage (blot, dot, or flame shaped), microaneurysm, hard exudates, and cotton wool spot
Malignant	Signs of moderate retinopathy plus papilledema

The staging of hypertensive retinopathy is based on retinal microcirculation pathological changes caused by the elevated blood pressure. An early change in the microcirculation of the retina as a response to the elevated blood pressure is a spasm of the blood vessels and an increase in the tension of the vascular smooth muscle, which presents as extensive retinal arteriostenosis clinically. Chronic hypertension results in chronic atherosclerotic lesions of the retinal microvessels, such as internal thickening of the retinal arteries, hyperplasia of the stroma, and hyaline degeneration. These manifest as diffuse or localized arteriolar stenosis, arteriolar wall opacity (copper wire- or silver wire-like arterial changes), and cross compression at the site of arteriovenous crossing. More significant elevation of blood pressure can lead to a damage of the blood–retinal barrier, resulting in the leakage of blood and lipid, clinically manifesting as superficial retinal hemorrhage and hard exudates, and the ischemia of nerve fiber layer leads to the formation of cotton

wool spots. When the blood pressure rises to a certain extent, increased intracranial pressure and accompanied optic nerve ischemia can cause optic disc edema. This optic neuropathy is usually called hypertensive optic neuropathy, and this usually indicates the occurrence of malignant hypertension [6].

It should be noted that hypertensive retinopathy does not progress step by step from grade 1 to grade 4 of the staging system. Some patients with a sudden onset of hypertension present retinal hemorrhages, optic disc, and macular edema without any retinal arteriosclerosis. In fact the stage 1 and 2 changes are usually seen in hypertensive patients with chronic high blood pressure, whose blood pressure elevation is not very dramatic; however in a radical hypertension or malignant hypertension patient, there is a sudden elevation of blood pressure, and the most common changes are stages 3 and 4. The European and WHO association of hypertension also considers the stage 3–4 hypertensive retinopathy to be of greater clinical significance, which indicates organ damage by elevated hypertension.

20.4 Evaluation of Retinal Vascular Diameter

The early evaluation of retinal vascular diameter is to assess the retinal arteriovenous ratio through ophthalmoscopy examination, which is still widely used in clinical practice. However, this method is too rough and difficult to quantify.

A lot of fundus camera and fundus photography are able to measure the point-to-point distance on the image and can be used to measure the diameter of the vessels; however, such a method also has some limitations, such as the difficulty to accurately define the vascular boundary on the image, inter-observer errors, and more time and manpower consumption.

In recent years, computer-assisted procedures have been commonly used in population-based studies to measure arterial and venous diameters. The most commonly applied software is Singapore I vessel vascular assessment (SIVA) and the vascular measurement software developed by Wisconsin-Madison University. Such software can accurately measure retinal vessel diameter in a certain area with good reproducibility and is important in population-based studies [7]. These methods measure retinal vascular diameter in similar ways, with only few differences. In general, first of all, each participant undergoes color fundus photography test, monocular or binocular, centered on the optic disc or macula, respectively. BDES, BMES, and EDC use the Zeiss FF3 camera, with a field view of 30°; ARIC and CHS use the Canon CR6-45NM camera, with a field view of 45°; RS uses the Topcon TRC-552 camera with a field view of 20°. Next, using the optic disc as the center, draw circles 0.5DD and 1DD away from the disc edge by the computer-aided software, and analyze the retinal vascular diameters within the annular region between the two circles. Finally, use various formulas, such as the Parr and Spears equation or the later Hubbard equation, to calculate the projected diameter of retinal vessels (by equivalent). In fact, these programs primarily provide three variables: the projected diameter of the central retinal artery (central retinal artery equivalent, CRAE), the projected diameter of the central retinal vein (central retinal vein equivalent CRVE), and the ratio of those two variables (arteriovenous ratio, AVR). Due to multiple influencing factors, the measurement result varies. SiMES reported that the mean central retinal artery diameter and mean central retinal vein diameter are 139.5 ± 15.7 μm and 219.3 ± 22.2 μm, respectively, in the Asian population.

With the development in OCT technology, some researches at home and abroad are trying to use OCT for vascular measurement. At present, the application is low, but with the improvement in OCT technology and image resolution it is possible to detect the structural changes of the retinal vascular wall caused by hypertension and help with a better understanding of the disease.

There are also some new commercial devices such as the dynamic vessel analyzer (DVA), which can be used to investigate the changes of retinal vascular wall under flash stimulation and to evaluate the function of endothelial cells [8]. The development of these new technologies and devices will also lead to a better understanding of the changes in retinal vessels under hypertension.

20.5 Correlation Between Retinal Vascular Diameter Changes and Coronary Heart Disease

The study of the relationship between retinal vascular diameter changes and coronary heart disease is mainly based on population-based studies mentioned above. The methods for measuring retinal diameter in these studies varied, so did their conclusions, some of which are even completely different.

20.5.1 Beaver Dam Eye Study (BDES)

This is a group of population-based studies conducted in Beaver Dam, Wisconsin. One cohort study showed no significant relation between the decrease of the arteriovenous ratio and the increase of the cardiovascular death rate [9]. However another case-control study in the same area found that the increase of the death rate of ischemic heart disease was related to the decrease of arteriovenous ratio in the branch site, poor separation angle, and lower artery tortuosity, and might be associated with the microcirculation damage and vascular endothelial dysfunction [10].

20.5.2 Cardiovascular Health Study (CHS)

The subjects in this study were over 65 from 4 different investigation centers in the United States. Results showed that, in the elderly population, after correcting factors like age, gender, race, blood pressure, blood glucose, and blood lipid, the widening of the retinal vein caliber was positively related to sudden coronary heart disease (rr = 3.0), and retinal artery stenosis also caused a high incidence of coronary heart disease (rr = 2.0) and an increase in the 5-year incidence [11]. In addition, for the elderly without any diabetes in these four communities, the prevalences of coronary heart disease and retinopathy were correlated (OR = 1.7), while local or extensive retinal artery stenosis, arteriovenous nicking index, and other index of atherosclerosis were not significantly correlated [12].

20.5.3 The Atherosclerosis Risk in Communities Study (ARIC)

In a survey of 9648 residents aged between 51 and 72 in 4 US communities, 84 women and 187 men had episodes of coronary heart disease after an average follow-up of 3.5 years. After controlling factors like the mean arterial pressure, diabetes, and smoking history, the decrease of AVR ratio was related to the increase of risk of coronary heart disease (rr = 1.37) in female population, while in male population there was no significant relationship (rr = 1.00). Therefore, microvascular lesions may play a more important role in the development of CHD in female population [13]. In another epidemic study of patients without diabetes, after correcting the differences of Framingham risk score, the widening of retinal vein caliber and artery stenosis were both high-risk factors for coronary disease attack in female population and indicated an increased risk of 10-year incidence, while the retinal caliber changes and coronary heart disease were not significantly related in the male population.

20.5.4 Multiethnic Atherosclerosis Study (MESA)

In a cross-sectional study of 5979 multiethnic residents in 6 American communities, retinal arteriovenous caliber was related to a series of cardiovascular risk factors, including hypertension, diabetes, obesity, and dyslipidemia. The venous caliber was also related to systemic inflammation [14]. In another survey conducted from 2002 to 2004, after controlling age, sex, blood pressure, diabetes, and smoking history, retinopathy and severe coronary artery calcification (CAC) score (OR = 1.43) were significantly related, and changes in retinal vessel caliber and CAC score were not significantly related [15]. A study of 212 subjects in one community in Minnesota showed that for asymptomatic adults of coronary artery calcification, retinal artery stenosis was related to a reduction of myocardial blood flow and perfusion, with some traditional cardiovascular risk factors also involved in regulation. This study suggested that retinal artery stenosis might be an indicator for coronary microvascular disease [16].

20.5.5 The Lipid Research Clinic Coronary Primary Prevention Trial (LRC-CPPT)

The lipid research clinic coronary primary prevention trial followed 560 middle-aged men with hypertension and hyperlipidemia, and the results showed that the existence of hypertension retinopathy indicated a doubled risk of coronary heart disease events; extensive or local arterial stenosis indicated a tripled risk of coronary heart disease. Yet this study did not use the standard fundus grading system to calculate retinal vessel caliber, but instead it used direct ophthalmoscope to assess whether there were damages to the retinal blood vessels (local or diffuse retinal artery stenosis, arteriovenous crossing, increased retinal artery reflection, etc.) [17].

20.5.6 Blue Mountain Eye Study (BMES)

In a study of 3654 middle-aged and senior residents in the Australia's Blue Mountain area, for those aged 49–75, the widening of retinal vein was related to CHD-induced death, and the RRs were 1.8 and 2.0 in men and women, respectively. For women of this age group, the decrease in AVR ratio and retinal artery stenosis also indicated an increased mortality associated with CHD, with RRs of 1.5 and 1.9, respectively [18].

20.5.7 Singapore Malay Population Eye Study (SiMES)

A cross-sectional study of 3280 Malaysians in Singapore found that, among Asian population, the retinal artery narrowing was related to hypertension, and the widening of venous caliber was related to the risk factors of cardiovascular disease such as smoking, dyslipidemia, high blood glucose, and high body mass index [19].

20.5.8 Rotterdam Study

A study of participants over 55 in Rotterdam, Holland, showed a variation in retinal vein caliber and that the widening of vessels was related to atherosclerosis, inflammation,

and blood cholesterol level, suggesting that it has a unique role in the prediction of coronary heart disease [20].

20.5.9 Wisconsin Epidemic Research (WES)

By examining patients with type 1 diabetes in Wisconsin, USA, it was found that a smaller AVR ratio was associated with death rate of myocardial infarction [21].

20.5.10 The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study

This is a prospective cohort study of type I childhood-onset diabetes in Pittsburgh, USA. A total of 448 participants without a history of retinal photocoagulation took part in the study. The results showed that only in the female population, the retinal artery thinning indicated an increased risk of coronary artery disease [22].

References

1. Delles C, Michelson G, Harazny J, et al. Impaired endothelial function of the retinal vasculature in hypertensive patients. Stroke. 2004;35(6):1289–93.
2. Klein R, Klein BE, Knudtson MD, et al. Are inflammatory factors related to retinal vessel caliber? The Beaver Dam Eye Study. Arch Ophthalmol. 2006;124(1):87–94.
3. Chester AH, Borland JA, Buttery LD, et al. Induction of nitric oxide synthase in human vascular smooth muscle: interactions between proinflammatory cytokines. Cardiovasc Res. 1998;38(3):814–21.
4. Wong TY, Mitchell P. Hypertensive retinopathy. N Engl J Med. 2004;351(22):2310–7.
5. Grosso A, Veglio F, Porta M, Grignolo FM, Wong TY. Hypertensive retinopathy revisited: some answers, more questions. Br J Ophthalmol. 2005;89(12):1646–54.
6. Wong TY, Mitchell P. The eye in hypertension. Lancet. 2007;369(9559):425–35.
7. Li LJ, Cheung CY, Chia A, et al. The relationship of body fatness indices and retinal vascular caliber in children. Int J Pediatr Obes. 2011;6(3–4):267–74.
8. Lim M, Sasongko MB, Ikram MK, et al. Systemic associations of dynamic retinal vessel analysis: a review of current literature. Microcirculation. 2013;20(3):257–68.
9. Wong TY, Knudtson MD, Klein R, et al. A prospective cohort study of retinal arteriolar narrowing and mortality. Am J Epidemiol. 2004;159(9):819–25.
10. Witt N, Wong TY, Hughes AD, et al. Abnormalities of retinal microvascular structure and risk of mortality from ischemic heart disease and stroke. Hypertension. 2006;47(5):975–81.
11. Wong TY, Kamineni A, Klein R, et al. Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the cardiovascular health study. Arch Intern Med. 2006;166(21):2388–94.
12. Wong TY, Klein R, Sharrett AR, et al. The prevalence and risk factors of retinal microvascular abnormalities in older persons: the Cardiovascular Health Study. Ophthalmology. 2003;110(4):658–66.
13. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA. 2002;287(9):1153–9.
14. Wong TY, Islam FM, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). Invest Ophthalmol Vis Sci. 2006;47(6):2341–50.
15. Wong TY, Cheung N, Islam FM, et al. Relation of retinopathy to coronary artery calcification: the multi-ethnic study of atherosclerosis. Am J Epidemiol. 2008;167(1):51–8.
16. Wang L, Wong TY, Sharrett AR, et al. Relationship between retinal arteriolar narrowing and myocardial perfusion: multi-ethnic study of atherosclerosis. Hypertension. 2008;51(1):119–26.
17. Duncan BB, Wong TY, Tyroler HA, et al. Hypertensive retinopathy and incident coronary heart disease in high risk men. Br J Ophthalmol. 2002;86(9):1002–6.
18. Wang JJ, Liew G, Wong TY, et al. Retinal vascular calibre and the risk of coronary heart disease-related death. Heart. 2006;92(11):1583–7.
19. Sun C, Liew G, Wang JJ, et al. Retinal vascular caliber, blood pressure, and cardiovascular risk factors in an Asian population: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci. 2008;49(5):1784–90.
20. Ikram MK, de Jong FJ, Vingerling JR, et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. Invest Ophthalmol Vis Sci. 2004;45(7):2129–34.
21. Klein BE, Klein R, McBride PE, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Arch Intern Med. 2004;164(17):1917–24.
22. Miller RG, Prince CT, Klein R, et al. Retinal vessel diameter and the incidence of coronary artery disease in type 1 diabetes. Am J Ophthalmol. 2009;147(4):653–60.

A Review of the Carotid Artery Stenosis and Ocular Ischemic Disease from the Perspective of Integrative Medicine

21

Ran Sun, Dachuan Liu, and Qi Zhou

21.1 Introduction

The carotid artery is the main blood vessel linking the heart, head, and face. Carotid artery stenosis is one of the most common causes of ischemic stroke. Ocular ischemic diseases are a group of diseases where pathophysiological changes are caused by ischemia of eye tissues. Many patients with carotid artery stenosis show symptoms of ocular ischemic diseases first and visit the ophthalmology department; no matter transient or persistence, patients with carotid stenosis who have ocular symptoms often have severe carotid artery stenosis already. From the perspective of ophthalmology, even though the etiology of ischemic ophthalmopathy is complex, they can all lead to pathological changes of retinal nerve tissues and vascular tissue. This makes early diagnosis difficult, and often requires repeated surgical treatments to rescue the remnant visual function in the advanced stage. From the perspective of integrative medicine, the anatomical homology of the carotid artery and ophthalmic artery determines their inseparable relationship; ocular ischemic disease is essentially a blood circulation disorder disease. We should look beyond the organs when analyzing it, and in the analysis of ocular blood circulation we should not only consider the terminal blood supply like the central retinal artery but also figure out the condition of the carotid artery. On the other hand, if we are studying the ocular ischemic syndrome in the view of integrative medicine, we will find that the essence is the decrease of blood supply from upstream vessels of ocular artery, i.e., the carotid artery. This will lead to a chronic or acute ischemia, not only the fundus but also the whole eye globe. Therefore, when considering treatment, we should jump out of the mindset of sub-disciplines and solve the fundamental problem. Other symptoms will also be easily solved in this way.

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21.2 The Anatomical Unity of the Carotid Artery and the Ocular Circulation

The carotid artery is the main facial blood supply from the heart, which consists of the external and internal carotid artery system. The external carotid artery system consists of the facial artery, the superior thyroid artery, the lingual artery, and the posterior auricular artery. The facial artery supplies the face, while the arteriae angularis and arteriae dorsalis nasi that branch from it supply part of the ocular adnexa. The first main branch of internal carotid is the ophthalmic artery, from which the central retinal artery system and the ciliary vascular system arise. These two systems contain the branches like central retinal artery, short posterior ciliary artery, and anterior ciliary artery, which supply blood for the anterior and posterior segments. The central retinal artery and the short posterior ciliary artery are the main vessels supplying the blood circulation of the retina and choroid.

Normally, the eye is supplied by the blood system described above, but in cases of carotid artery stenosis and a reduced eye perfusion pressure the body can open the collateral circulation of external carotid artery and ophthalmic artery, allowing a retrograde flow of blood into the ophthalmic artery to compensate. The effective establishment and opening of collateral circulation depend on the integrity of collateral vessels and change of pressure gradient and can only occur to compensate the blood supply when the pressure decrease of the antegrade flow from the internal carotid artery to the ophthalmic artery is not high enough to offset the pressure of collateral vessels of external carotid artery and ophthalmic artery [1–3].

In conclusion, in analyzing the ocular circulation, we should not only consider the terminal blood supply of the

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_21

arteries like the central retinal arteries and the ciliary arteries, but also explore the condition of the carotid arteries, and even the collateral circulation between the eye and the brain. We should explore the anatomical changes of the ocular blood circulation from an integrative medicine's perspective.

21.3 Evidences for the Unity of Carotid Artery Stenosis and Ocular Ischemic Syndrome

Ocular ischemic diseases include retinal vascular embolism, diabetic retinopathy, hypertensive retinopathy, ischemic optic neuropathy, and Eales disease, which are mainly caused by pathological changes of the supplying vessels and will result in disturbances of ocular blood circulation and affect the retinal function [4]. The pathological changes can occur in the terminal blood vessels that supply the eyeballs (e.g., the central retina artery and the short posterior ciliary arteries), or in the larger vessels (e.g., the ophthalmic artery and carotid artery). From the perspective view of integrative medicine, even when a clear diagnose of ocular terminal vascular disease (such as diabetic retinopathy, Eales disease) was made, the overall blood perfusion decrease in the eyes caused by macro-vascular anomaly (e.g., carotid stenosis) as the underlying influence factor could not be neglected [5]. Although the anatomic unity of the carotid artery and the blood circulation constitutes the pathologic basis for carotid stenosis and ocular ischemic diseases, the correlation between the carotid artery stenosis and the incidence of ocular ischemic disease still needs further validation.

The current diagnostic methods for carotid artery stenosis are the noninvasive color duplex flow imaging (CDFI) and the invasive digital subtraction angiography (DSA). These methods can show location and degree of the stenosis, the plaque attached to the wall, and are the main techniques in studying carotid artery stenosis and ocular ischemic disease.

DSA is currently the golden standard for diagnosing carotid artery stenosis [6, 7]; it calculates the degree of carotid artery stenosis by directly measuring the remnant intravascular diameter. The DSA technology can also give a better image of the ocular artery when checking macro-vessels like the carotid artery. It is useful for the understanding of the anatomy of the carotid artery and ophthalmic artery and revealing the relationship between carotid artery stenosis and ocular ischemic disease. At present, DSA is unable to satisfactorily display the terminal blood vessels of the eye, like the central retinal artery and ciliary artery, but with the improvement of the intravascular angiography technique and material DSA will be able to better evaluate the terminal blood vessels, which will in turn improve our understanding of the formation and function of ocular collateral circulation during carotid artery stenosis.

As a noninvasive ocular vascular examination technique with good repeatability, CDFI has great advantages in assessing and diagnosing vascular diseases. Based on the anatomy of the orbital cavity, CDFI can locate the main vessels (e.g., the ophthalmic artery, central retinal artery, and posterior ciliary artery) accurately and not be affected by medicine or the refractive media. This technique provides us with both qualitative and quantitative hemodynamic information. It can provide parameters like peak systolic velocity (PSV) and end-diastolic velocity (EDV). PSV demonstrates the degree of vascular filling and blood supply, and a drop of this index represents a supply deficiency; EDV reveals the perfusion condition of terminal tissues, and a drop represents insufficient blood supply for the distal tissues. In recent years, with the development of CDFI technology, the relationship between carotid artery stenosis and ocular ischemic disease is better understood, and evidences for the influences of carotid artery stenosis on the ocular blood circulation are more convincing. First, when percentage of carotid artery stenosis is over 90%, the detected perfusion pressure of central retinal artery decreases by more than 50% [8]. Second, when percentage of carotid artery stenosis is more than 50%, the peak velocity and the diastolic velocity of central retinal artery decrease, with a significant increase of resistance index [9]. Third, increase of blood flow resistance can be detected in the central retinal artery when mild stenosis of carotid artery exists, causing ocular perfusion difficulties [10].

The above CDFI and DSA techniques can be used to investigate the relationship between carotid stenosis and ocular ischemic diseases, and to a certain extent demonstrate the unity of the two diseases. On the other hand, by observing the changes of ocular ischemia symptoms and ocular blood circulation after the treatment of carotid stenosis, we can further explore the unity of carotid stenosis and ocular ischemic diseases.

Clinically, the most direct and effective technique treating severe carotid artery stenosis is surgery, i.e., carotid endarterectomy (CEA) and carotid artery stenting (CAS). By monitoring the postoperational improvement of symptoms of ocular ischemic disease and changes in ocular blood flow, the unity of carotid artery stenosis and ocular ischemic disease can also be proved from a different view. Marx et al. performed CEA on patients with ocular ischemic syndrome caused by carotid artery stenosis. They found that the ocular ischemia symptoms (including the loss of vision, amaurosis fugax, blurred vision, etc.) disappeared after the surgery [11]. Ishikawa et al. reported that after CEA, carotid stenosis was resolved; the retrobulbar blood flow increased in the ipsilateral eye; the peak systolic and end-diastolic velocity of the ophthalmic artery, the central retinal artery, and the

temporal posterior short ciliary artery were significantly increased; at the same time, the resistance index decreased significantly; and the fundus ischemic changes improved [12]. Marx et al. also evaluated the effect of CAS surgery on ocular circulation and chronic ocular ischemia [11]. In the 38 ocular ischemic syndrome patients with stenosis greater than 80% in the origin of carotid artery, retrograde ophthalmic artery flow changed to antegrade flow after surgery in 13. The average peak velocity of all the ophthalmic arteries increased significantly 24 h after surgery in all patients. After an average of 2.8 years of follow-up after surgery, visual acuity was improved in seven cases and the mean pressure of the retinal artery and arm retinal circulation time were significantly improved. They also reported three cases in which the intracranial perfusion increased after CAS surgery, of which fundus fluorescein angiography showed a shortened arteriovenous transit time in two cases, correction of retrograde flow of ophthalmic artery in one case, and stable or improved visual acuity in all the three cases. Ho et al. reported one ocular ischemia syndrome patient with 90–95% stenosis of bilateral internal carotid artery. One month after bilateral CAS, the visual acuity increased from 0.4 to 1, and retinal hemorrhage was completely absorbed 6 months after surgery [13]. The improvement of ischemic symptoms or the hemodynamic parameters after carotid stenosis resolved reported in the above study showed that the stenosis of carotid artery is closely related to the occurrence of ischemic ocular diseases [14, 15].

In conclusion, the evidences of the unity carotid stenosis and ocular ischemic disease are reminders for ophthalmologists to have a holistic view on ocular ischemic diseases.

21.4 Carotid Artery Stenosis and Ocular Ischemic Syndrome

Ocular ischemic syndrome (OIS) is an anterior and posterior ischemic disease caused by the reduction of ocular perfusion due to carotid stenosis or occlusion [16]. It is usually found in males over the age of 50 [17]. The mean age of onset is (63 ± 8) years [18]. It is a severe form of ocular ischemic disease, and 2/3 patients with OIS have moderate-to-severe carotid stenosis [16, 19]. Therefore, OIS is closely related to carotid stenosis, and is described here.

OIS can be divided into acute and chronic ischemia based on pathogenesis. At present, the pathogenesis of ocular ischemia caused by carotid stenosis is considered to be two-faceted: (1) plaque detaches in the narrowed artery and leads to central retinal artery embolism, which will cause an acute ischemia of retinal artery circulation [20], and (2) the carotid atherosclerosis narrowing causes a decrease in ocular perfusion pressure, and the chronic retinal hypoperfusion will lead to a chronic ischemia [21, 22].

This disease is often misdiagnosed, because OIS often occurs in the elderly, who usually have other systemic diseases like diabetes and hypertension, and the symptoms of this disease are similar to diabetic retinopathy, retinal venous occlusion, and hypertensive retinopathy [23–26].

Therefore, it is important to screen the carotid artery in the early stage of ocular ischemia. It helps the diagnosis and management of OSI [27].

Since the main causes of OIS are carotid stenosis or occlusion, there is a close relationship between the prognosis and treatment of carotid artery stenosis. The studies of Costa et al. [28] and Kawaguchi et al. [29] showed that after CEA, the retrobulbar blood flow and the visual acuity improved, and no vision loss occurred again after the 32-month follow-up. Ishikawa et al. [12] and Kozobolis et al. [30] also reported the effectiveness of CEA in preventing further ocular ischemia and improving ocular blood flow in OIS patients. On the contrary, Sivalingam et al. [31] followed 17 cases of OIS patients who had CEA 1 year ago. The study found that vision improved in 7% patients, was stable and unchanged in 33%, and was still worsening in 60%. Mizener et al. [32] also carried out a comparative study of OIS patients with and without CEA and found that there was no significant difference in visual acuity between the two groups. The efficacy of CAS as an alternative for the high-risk CEA in improving OIS is on the debate. Although Marx [11] and Ho [13] believed that CAS could improve ocular blood supply in OIS patients, many scholars are still questioning the efficacy of CAS on preventing the onset and progression of OIS, considering the current small sample size and short follow-up time of these studies [11, 13, 20, 33, 34]. A review of the debate on the prognosis of OIS surgeries (including CEA and CAS) suggested that OIS is a severe form of ocular ischemic disease, which is different from the general ocular ischemic diseases and is closer related to carotid artery stenosis. On the one hand, after resolving carotid artery stenosis, the ocular blood supply will improve and the OIS symptoms will disappear with visual function recovered partially; on the other hand, due to the persistent low perfusion, the ocular nerve tissues have been severely damaged, so even after alleviation of the carotid artery stenosis and ocular ischemia, visual function cannot be restored.

In conclusion, the divergent opinions about the impact of carotid artery stenosis on OIS onset, progression, and prognosis also demonstrate a close relationship between them. They should not be separated during diagnosis and treatment. It is important to pay attention to early detection of ocular blood changes in patients with carotid artery stenosis and treat OIS in a holistic way. Both ophthalmologists and neurologists should establish an integrative medicine concept to avoid the wrong practice of "treating only where the pain is."

21.5 Conclusion

With the aging of population, the incidence of cardiovascular diseases has increased year by year. According to statistics, the incidence of carotid atherosclerosis in the elderly over 60 is up to 10% of the population [35]. The incidence of ocular ischemic disease has increased year by year as well because of the close relationship between the carotid artery and the blood supply of the eye. It is key for ophthalmologists and neurologists to pay attention to systemic pathology of ocular ischemic disease and to establish an integrative concept of medicine.

References

1. Li XP, Zhang B. Relationship of cerebral infarction with carotid atherosclerosis and blood-lipid. J Mod Med. 2004;14(21):137–8.
2. Hendrikse J, Hartkamp MJ, Hillen B, et al. Collateral ability of the circle of Willis in patients with unilateral internal carotid artery occlusion: border gone infarcts and clinical symptoms. Stroke. 2002;32(12):2768–73.
3. Telman G, Kouperberg E, Spreeher E, et al. Assessment of ophthalmic artery collateral path way in the hemispheric cerebral hemodynamics in patients with severe unilateral carotid stenosis. Neurol Res. 2003;25(3):309–11.
4. Ge J, Zhao JL, Cui H. Ophthalmology. Beijing: People's Medical Publishing House; 2005. p. 88–93.
5. Hsu HY, Yang FY, Chao AC, et al. Distribution of carotid arterial lesions in Chinese patients with transient monocular blindness. Stroke. 2006;37(2):531–2.
6. Dhonge M, De Laey JJ. The ocular ischemic syndrome. Bull Soc Belge Ophthalmol. 1989;231:1–13.
7. Holdswomh R, MeCollum PT, Bryce JS, et al. Symptoms, stenosis and carotid plaque morphology. Vasc Endovasc Surg. 1995;9(1):80–5.
8. Kobayashi S, Hollenhorst RW, Sundt TM Jr. Retinal arterial pressure before and after surgery for carotid artery stenosis. Stroke. 1971;2:569–75.
9. Jacobs NA, Trew DR. Occlusion of the central retinal artery and ocular neovascularisation: an indirect association? Eye (Lond). 1992;6(6):599–602.
10. Huang SM, Xiong X, Tong YY, et al. Color Doppler in detection of blood flow of the ophthalmic artery in patients with carotid atherosclerosis. Chin J Ocular Fundus Dis. 2001;17(2):150–1.
11. Marx JL, Hreib K, Choi TS. Percutaneous carotid artery angioplasty and stenting for ocular ischemic syndrome. Ophthalmology. 2004;111(12):2284–91.
12. Ishikawa K, Kimura I, Shinoda K, et al. In situ confirmation of retinal b1ood flow improvement after carotid endarterectomy in a patient with ocular ischemic syndrome. Am J Ophthalmol. 2002;134(2):295–7.
13. Ho TY, Lin PK, Huang CH. White centered retinal hemorrhage in ocular ischemic syndrome resolved after carotid artery stenting. J Chin Med Assoc. 2008;71:270–2.
14. Rennie CA, Flanagan DW. Resolution of proliferative venous stasis retinopathy after carotid endarterectomy. Br J Ophthalmol. 2002;86:117–8.
15. Rose L, Zamir E. Reversite anterior segment ischaemia after carotid endarterectomy. Clin Exp Ophthalmol. 2007;35:94–5.
16. Lawrence PF, Oderich GS. Ophthalmologic findings as predictors of carotid artery disease. Vasc Endovascular Surg. 2002;36(6):415–24.
17. Alizai AM, Trobe JD, Thompson BG, et al. Ocular ischemic syndrome after occlusion of both external carotid arteries. J Neuroophthalmol. 2005;25:268–72.
18. Chen KJ, Chen SN, Kao LY. Ocular ischemic syndrome. Chang Gung Med J. 2001;24(8):483–91.
19. Munch IC, Larsen M. [The ocular ischemic syndrome]. Ugeskr Laeger. 2005;167:3269–73.
20. Kawaguchi S, Sakaki T, Iwahashi H, et al. Effect of carotid artery stenting on ocular circulation and chronic ocular ischemic syndrome. Cerebrovasc Dis. 2006;22:402–8.
21. Tang WQ, Wei SH, Li S, et al. A clinical analysis of the ocular manifestations associated with carotid stenosis. Chin J Ocular Fundus Dis. 2006;22(6):376–8.
22. Foncea Beti N, Mateo I, Diaz La Calle V, et al. The ocular ischemic syndrome. Clin Neurol Neurosurg. 2003;106:60–2.
23. Bigou MA, Bettembourg O, Hebert T, et al. Unilateral ocular ischemic syndrome in a diabetic patient. J Fr Ophthalmol. 2006;29:e2.
24. Chen CS, Miller NR. Ocular ischemic syndrome: review of clinical presentations, etiology, investigation, and management. Compr Ophthalmol Updat. 2007;8:17–28.
25. Welch HJ, Murphy MC, Raftery KB, et al. Carotid duplex with contralateral disease: the influence of vertebral artery blood flow. Ann Vasc Surg. 2000;14:82–8.
26. Klijn CJ, Kappelle LJ, van Schooneveld MJ, et al. Venous stasis retinopathy in symptomatic carotid artery occlusion: prevalence, cause, and outcome. Stroke. 2002;33:695–701.
27. Wang YL, Zhao L, Li M. Improved circulation in ocular ischemic syndrome after carotid artery stenting. Chin Med J. 2011;124(21):3598–600.
28. Costa VP, Kuzniec S, Molnar U, et al. The effects of carotid endarterectomy on the retrobulbar circulation of patients with severe occlusive carotid artery disease: an investigation by color Doppler imaging. Ophthalmology. 1999;106:306–10.
29. Kawaguchi S, Okuno S, Sakaki T, et al. Effect of carotid endarterectomy on chronic ocular ischemic syndrome due to internal carotid artery stenosis. Neurosurgery. 2001;48:328–33.
30. Kozobolis VP, Detorakis ET, Georgiadis GS, et al. Perimetric and retrobulbar blood flow changes following carotid endarterectomy. Graefes Arch Clin Exp Opthalmol. 1957;43(4 part 1):583–9.
31. Sivalingam A, Brown GC, Magargal LE. The ocular ischemic syndrome. III. Visual prognosis and the effect of treatment. Int Ophthalmol. 1989;15(1):15–20.
32. Mizener JB, Podhajsky P, Hayreh SS. Ocular ischemic syndrome. Ophthalmology. 1997;104(5):859–86.
33. Nussbaumer-Ochsner Y, Eberli FR, Baumgartner RW, et al. Sirolimus-eluting stenting of the external carotid artery for the treatment of ocular ischemia. J Endovasc Ther. 2006;13(5):672–5.
34. Onizuka M, Masuya N, Miyazaki H. [Placement of stent for internal carotid artery stenosis in the cervical portion improved ocular ischemic syndrome]. No To shinkei. 2001;53(7):679–82.
35. Luo RJ, Liu SR, Li XM, et al. Fifty-eight cases of ocular ischemic diseases caused by carotid artery stenosis. Chin Med J (Engl). 2010;123(19):2662–5.

The Establishment of Interdisciplinary Comprehensive Diagnosis Model for Ocular Ischemia Syndrome

22

Yanling Wang and Yun Feng

22.1 Introduction

Ocular ischemic syndrome is a clinical syndrome with a series of brain and eye symptoms caused by chronic severe carotid artery stenosis or occlusion. Atherosclerosis is the most common cause. Therefore, it is particularly important to prevent and treat more serious ischemic cardiovascular and cerebrovascular diseases while reducing visual impairment. Based on the complexity of integration, multi-disciplinary comprehensive diagnosis and treatment model is the direction to solve the current problems in the treatment of ocular ischemic syndrome. After reading this chapter, we can better understand the new concept of clinical multidisciplinary comprehensive diagnosis and treatment mode. As far as ocular ischemic syndrome is concerned, the diagnosis and treatment should be carried out by a team of ophthalmologists, cardiologists, neurologists, neurosurgeons, vascular surgeons and interventional radiologists. Only in this way can patients get the best treatment in time, and avoid or alleviate the occurrence of life-threatening systemic ischemic diseases while saving their eyesight.

Ocular ischemic syndrome (OIS) is a series of brain and eye symptoms caused by carotid artery occlusion or stenosis which covers ophthalmology, neurosurgery and other disciplines. Its 5-year mortality rate is as high as 40% [1, 2]. However, because of the occult onset of OIS and the different severity of ischemia, the ocular and systemic manifestations are complex and varied, and it is easy to be misdiagnosed or missed in clinic. Nevertheless, as an important organ that directly reflects the circulatory state, the ocular manifestation may be the earliest in the local or systemic manifestations of OIS and have a "warning" effect on the ischemic damage of other organs in the whole body. Therefore, ophthalmologists should, first of all, pay adequate attention to the clinical manifestations and hazards of OIS. In addition, the basic cause of OIS is carotid artery occlusion or stenosis, so the diagnosis and treatment require the cooperation of different disciplines, such as ophthalmology and neurology, and also the department of cardiology. Against the background of the traditional medical division where disciplines and departments are established based on organ, how to establish a new model of multidisciplinary comprehensive diagnosis and treatment based on patient history, clinical manifestations, and related examinations, to improve the standard of diagnosis and treatment of OIS is an important problem that we must face.

22.2 Problems Faced in OIS Research

Hollenhorst [3] reported that fundus changes were found in 15 out of 124 patients with internal carotid artery occlusion or stenosis. OIS rarely can be caused by occlusion of the lumen of the external carotid artery or the aortas of the higher level, namely the aortas originating from the aortic arch, such as the subclavian artery [4]. Kearns and Hollenhost [5] called this type of fundus change as stasis retinopathy. According to Hedges, this fundus' change is not due to venous congestion, but due to long-term insufficient ocular artery perfusion resulting in carotid artery obstruction or stenosis, which is more appropriate to be called hypoperfusion retinopathy [6]. Later, researchers found that in addition to fundus changes, these patients also had anterior ocular lesions, optic neuropathy, brain and systemic symptoms, so they were called OIS more comprehensive [7–9]. With the increase in the depth of research of OIS in recent years, it is found that atherosclerosis is the most common cause of internal carotid artery stenosis or occlusion [10]; the possible mechanisms of OIS include

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_22

microembolus movement, vasospasm, and hemodynamic insufficiency [11], but further exploration is still needed since its specific mechanism is unknown yet.

Transcranial Doppler ultrasound (TCD) has good sensitivity and specificity in the diagnosis of the site and the severity of stenosis or occlusion of the initial segment of the internal carotid artery and the status of the cerebral collateral circulation, so it is a reliable method for diagnosis of cerebral and carotid vascular stenosis or occlusion at present [12]; magnetic resonance angiography (MRA) can show the changes in the morphology and diameter of the great vessels in the neck and the brain; digital subtraction angiography (DSA) is the gold standard for definite diagnosis of carotid artery stenosis, but the DSA is traumatic with a certain level of risk: Therefore, more and more attention has been paid to non-invasive examination methods such as TCD and MRA. However, these methods cannot accurately or qualitatively analyze the severity and range of carotid stenosis and the relationship between OIS and carotid stenosis. Therefore, the development of new technology and method that can accurately assess and quantify the severity and range of carotid stenosis and its relationship with OIS is the first problem that needs to be solved if early diagnosis and rational intervention for OIS are to be achieved.

There are many controversies about the treatment of OIS. At present, the main interventions for carotid stenosis are drugs, carotid stent implantation (CAS), carotid endarterectomy (CEA), and so on. The choice of treatment is often based on the severity of carotid stenosis, patient age, and systemic condition. Conventional drug treatment had no obvious effect on OIS. There are also many uncertainties in the therapeutic effect of treatment of carotid stenosis by different surgical interventions on OIS. Studies have shown that although surgery improves brain and ocular blood supply, the vision acuity does not get improved [13–15]. It was also suggested that an uncertain or even no effect was produced with interventional or surgical treatment in nearly 20% of patients [16]. To explore a simple and convenient surgical intervention to improve OIS ischemia status and promote visual recovery with fewer complications are other problems to be solved.

About 73% of patients with OIS had hypertension, 56% had diabetes, and 19% had peripheral vascular disease [2]. The 5-year mortality rate was 40%, and the most common cause of death was cardiovascular and cerebrovascular events. Among them, cardiovascular disease (mainly myocardial infarction) accounted for 63%, cerebral infarction accounted for 19%, and incidence of diabetes increased significantly [2, 17, 18]. Therefore, it is a serious problem how to prevent more serious ischemic cardiovascular or brain diseases for OIS patients seeking treatment first in ophthalmology for visual impairment, and enough attention should be paid to this in clinical diagnosis and treatment of OIS.

22.3 The Multidisciplinary Comprehensive Diagnosis and Treatment Model, the Future Direction for Solving the Problems in OIS Research

22.3.1 Construction of a Clinical Multidisciplinary Diagnosis and Treatment Model

The traditional medical model is often limited to a single department, which can not provide a comprehensive diagnosis and treatment strategy, and can not meet the needs of both doctors and patients. The clinical multidisciplinary team (MDT) is a brand new concept as compared with the traditional disease diagnosis and treatment model. It is a clinical diagnosis and treatment model in which experts usually from more than two related disciplines form a relatively fixed panel to exchange diagnosis and treatment opinions on the diseases of an organ or a system through regular meetings at a fixed place. MDT has become an important mode of disease diagnosis and treatment in large hospitals abroad. MDT treatment patterns have been established in some important cancer treatment centers in the United States and other countries. In the UK, the NHS cancer plan has included the MDT treatment model for rectal cancer [19]. In Germany and other countries where medical centers are relatively concentrated, the MDT model has become an important part of the hospital medical system.

In the past, ophthalmologists have been the main players in OIS diagnosis and treatment; but with the better understanding of the disease, multidisciplinary collaboration has become necessary for the diagnosis and treatment of the disease. Modern OIS diagnosis and treatment must be completed collaboratively by the departments of ophthalmology, cardiology, neurology, neurosurgery, vascular surgery, interventional radiology, and many other work teams. To form such a work pattern in line with the modern concept of OIS multidisciplinary diagnosis and treatment, first of all, medical staff of related disciplines should be fully aware of the importance of the MDT model in the diagnosis and treatment of OIS and promote and actively participate in this model from the perspective of academic development; on this basis, administrative departments of hospitals should guide and fully support the MDT model through system design and resource allocation, by formulating standards and providing the necessary space, time, and material security. In this way, a clinical multidisciplinary treatment team may be established and multiple disciplines be effectively mobilized to provide the optimal treatment for individual patients based on the actual case situation, clinical experiences of each discipline, and evidence-based clinical case discussion. The timeliness and continuity of

consultations and the fact that it's the shared responsibility of multiple disciplines to treat a patient should be stressed, and the advanced technologies of each of the multiple disciplines should be used in time, so that the OIS patients will get the best treatment in a timely manner, with the patients' vision saved and the occurrence of life-threatening systemic ischemic diseases avoided or reduced at the same time.

The multi-disciplinary diagnosis and treatment mode from "patient seeking doctor" to "doctor seeking patient" is a challenge to the traditional specialist diagnosis and treatment mode. The clinical departments and the medical technology departments will jointly read examination images and make decisions based on discussion, and thus the timeliness and continuity of treatment of OIS patients are improved thanks to the pooled rich clinical experience of the experts from multiple disciplines which facilitates definite diagnosis and prevents good treatment opportunities from being missed. While bringing real benefits to patients, this will also help doctors have a better understanding of the integrated nature of disease and the new progress in the relevant departments.

22.3.2 The Establishment of a Multidisciplinary One-Stop Service Medical System

The term "one-stop service" means not only the change of service quantity, but also the improvement of service quality. Theoretically, "one-stop service" is integration of services. It can be either the integration of service process or the integration of service content [20]. The "one-stop" multidisciplinary treatment system integrating the related departments can shorten the waiting time of patients, streamline treatment process, and improve treatment rate.

In the "one-stop" multidisciplinary treatment model for OIS, once suspected cases are found, regardless of whether the patient was received by ischemic ocular disease clinic or by cardiovascular specialist outpatient clinics, the OIS diagnosis and treatment process will be initiated. After necessary examinations are completed, ophthalmology experts and experts from multiple related disciplines will systematically analyze the disease, make the definite diagnosis, and develop the best treatment plan together, which is really convenient for patients and shortens the diagnosis and treatment time and provides the best chance to save the visual function and quality of life of patients. This will realize the integration of medical resources to best meet the needs of patients, and thus the best embodiment of the "patient-centric" service concept.

22.3.3 Standardization of OIS Diagnosis and Treatment Process and Establishment of OIS Patient Database

OIS is a disease involving multiple systems and multiple organs. It is imperative to establish a database of OIS patients. The establishment of OIS database makes the clinical data unified and standardized and makes it convenient to conduct clinical data inquiry, collection, classification, and statistical analysis. It will facilitate patients' follow-up and clinical experience summarization to improve the quality of medical treatment. To build a good OIS database, you must understand the relevant issues involved in the current OIS diagnosis and treatment process and norms.

First visit: The general condition of patients, medical history, laboratory tests, risk factors, and target organ damages of the clinically suspected OIS patients should be put into the database.

Screening: Fundus fluorescein angiography should be performed to evaluate ocular lesions caused by ischemia; perform TCD, CT angiography or MRA, and if necessary DSA to find the cause and treatment basis; and blood pressure, blood glucose, and blood lipid and related laboratory examinations should also be performed to evaluate the general condition.

Diagnosis: Put together medical history, symptoms, signs, and other examination results, contact MDT experts from relevant departments, including the department of neurology, department of cardiology, department of neurosurgery, vascular surgery, and interventional radiology for consultation. Some special types of vascular diseases should be ruled out at the same time, such as giant cell arteritis and Takayasu's arteritis. The severity of ischemic target organ involvement is evaluated collectively by all disciplines. The above data are all entered into the database.

Treatment: The treatment of ocular ischemic syndrome is mainly to treat the ocular ischemic complications to delay the progression of ocular ischemia, to identify and control risk factors for vascular disease, and to perform surgery at the right time, thereby reducing cardiovascular and cerebrovascular accident. According to the severity of the disease, different treatment options are adopted: (1) etiological treatment: for patients without target organ damage or operation indications, the cause of the disease is the key to the treatment. Control of hypertension and reduction of blood pressure by 10/5 mmHg (1 mmHg = 0.133 kPa) are beneficial. Control diabetes by controlling blood sugar near normal levels to reduce microvascular complications, and glycosylated hemoglobin should be <7% during treatment. Control hyperlipidemia, and the target level of serum lipids is low-density lipoprotein cholesterol (LDL-C) <2.58 mmol/L, and

LDL-C <1.81 mmol/L for high-risk patients. The patients should stop smoking and alcohol, and control weight, to control basal metabolic rate to a body mass index of 18.5–24.9 kg/m^2. Vasospasm is believed to be a cause of OIS and it has been reported that treatment of OIS with calcium channel blocker verapamil resulted in visual acuity improvement, iris neovascularization decrease, and lower intraocular pressure [21]. (2) Surgical treatment: Carotid stenosis is the most important cause of ocular ischemia syndrome. Relieving the stenosis of internal carotid artery and restoring the blood perfusion of eyeballs with surgical interventions can improve the visual function to some extent. CEA has good effect for early OIS patients with a carotid artery stenosis degree larger than 70% without neovascular glaucoma [22]. CAS is mainly used for CEA contraindicated patients. Extracranial-intracranial arterial bypass is to slow the development of brain ischemia through anastomosis of superficial temporal artery and middle cerebral artery branches to increase the amount of blood supply to the brain, which is suitable for total occlusion of carotid artery or internal carotid artery or stenosis of the internal carotid artery whose site is not easy for surgery. It has certain therapeutic effect for the ocular symptoms. (3) Ocular treatment: The main purpose of ocular treatment is to control the anterior segment inflammation and improve local retina ischemia to prevent neovascular glaucoma. For patients with retinal ischemia, laser photocoagulation can effectively control ocular neovascularization and prevent the occurrence neovascular glaucoma [18]; panretinal cryotherapy will help control the disease when the fundus does not allow laser photocoagulation [23, 24]. Intravitreal injection of anti-VEGF drugs provides a new way for neovascular glaucoma treatment. The local treatment of compound anisodine is mainly to improve the ocular blood circulation to protect the optic nerve and save the visual acuity.

Follow up: Establish a health record for each patient and provide education, counseling, regular examination, and follow-up. Each visit is followed by a treatment plan based on the patient's condition and the patient should be informed of the time and items for the next follow-up. For patients who are critically ill, more frequent visits and examinations are needed. Regular examination and follow-up are especially important for OIS patients. The patients should be informed of the importance of regular examination and follow-up and regularly notified to improve their compliance with test and treatment protocol and prevent the progression of the lesions. Establishment of service information communication channels through the network system will enable distant patients to upload their examination data at any time, so that MDT experts can remotely provide individualized diagnosis and treatment and health guidance for them based on these previous data. In this way, their treatment is more standardized, geographical restrictions are eliminated, and sharing of medical resources is truly realized. The data are timely, synchronous, and easy to operate and can be monitored for life, making it more convenient to conduct retrospective analysis to evaluate the original diagnosis and treatment system to gradually improve the OIS disease management model.

The database can be used for clinical research to guide the clinical work and connected to the computer network at the same time to provide data for the relevant agencies and peers for data sharing to facilitate academic exchange and mutual improvement [25].

22.4 Future Development

Under the traditional medical division model in which disciplines and specialties are established based on the organs, OIS research faces many unavoidable problems and challenges. The new multidisciplinary diagnosis and treatment model is the direction for solving the problems in OIS research. Construction of clinical multidisciplinary treatment model, establishment of a multidisciplinary one-stop diagnosis and treatment system, standardization of OIS diagnosis and treatment process, establishment of OIS patient database, and construction of a new clinical, research, and teaching platform will help us explore the occurrence and progression pattern of OIS and utilize the advanced treatment technology in multiple disciplines, so that the OIS patients will get the best treatment, with the vision saved and the occurrence of life-threatening systemic ischemic diseases avoided or reduced as well. Although the construction of a multidisciplinary comprehensive diagnosis and treatment model is a systematic project involving many factors, the transformation of medical mode and the progress of medical technology have shown the dawning light of this trend. Let's actively participate in and promote this transformation, making joint efforts to improve the diagnosis and treatment of OIS.

References

1. Wang YL. Basics of ocular ischemia syndrome. Diagnosis and treatment of ocular ischemia syndrome. Beijing: People's Military Medical Press; 2012. p. 1–20.
2. Sivalingam A, Brown GC, Magargal LE, et al. The ocular ischemic syndrome: II: mortality and systemic morbidity. Int Ophthalmol. 1989;13:187–91.
3. Hollenhorst RW. Ocular manifestations of insufficiency or thrombosis of the internal carotid artery. Am J Ophthalmol. 1959;47:753–67.
4. Alizai AM, Trobe JD, Thompson BG, et al. Ocular ischemic syndrome after occlusion of both external carotid arteries. J Neuroophthalmol. 2005;25:268–72.
5. Kearns TP, Hollenhorst RW. Venous stasis retinopathy of occlusive disease of the carotid artery. Proc Staff Meet Mayo Clin. 1963;38:304–12.
6. Hedges TR Jr. Ophthalmoscopic findings in internal carotid artery occlusion. Bull Johns Hopkins Hosp. 1962;3(111):89–97.

7. Young LH, Appen RE. Ischemic oculopathy: a manifestation of carotid artery disease. Arch Neurol. 1981;38:358–61.
8. Brown GC, Magargel LE. The ocular ischemic syndrome: clinical, fluorescein angiographic and carotid angiographic features. Int Ophthalmol. 1988;11:239–51.
9. Guo T, Zhang HR. Clinical features and carotid color ultrasonic Doppler characteristics of ocular ischemic syndrome. Chin J Ophthalmol. 2011;47:228–34.
10. Paraskevas KI, Mikhailidis DP, Liapis CD. Internal carotid artery occlusion: association with atherosclerotic disease in other arterial beds and vascular risk factors. Angiology. 2007;58:329–35.
11. Mendrinos E, Machinis TG, Pournaras CJ. Ocular ischemic syndrome. Surv Ophthalmol. 2010;55:2–34.
12. Wu ZY, Yang HS, Li XM. The application of color Doppler ultrasound system in intraocular lesions. Chin J Ophthalmol. 1997;33:88–90.
13. Havelius U, Bergqvist D, Hindfelt B, et al. Improved dark adaptation after carotid endarterectomy: evidence of a long-term ischemic penumbra. Neurology. 1997;49:1360–4.
14. Costa VP, Kuzniec S, Molnar LJ, et al. The effects of carotid endarterectomy on the retrobulbar circulation of patients with severe occlusive carotid artery disease. Ophthalmology. 1999;106:306–10.
15. Wolintz RJ. Carotid endarterectomy for ophthalmic manifestations: is it ever indicated? J Neuroophthalmol. 2005;25:299–302.
16. Liu SR, Luo RJ, Li XM, et al. Clinical features of carotid stenosis with ocular ischemic manifestations and therapeutic effects. Chin J Ocular Fundus Dis. 2010;26:310–3.
17. Mizener JB, Podhajsky P, Hayreh SS. Ocular ischemic syndrome. Ophthalmology. 1997;104:859–64.
18. Chen KJ, Chen SN, Kao LY, et al. Ocular ischemic syndrome. Chang Gung Med J. 2001;24:483–91.
19. Sharma A, Sharp DM, Walker LG, et al. Colorectal MDTs: the team's perspective. Colorectal Dis. 2007;10:63–8.
20. Qian YP. Preliminary experience of our hospital in one-stop outpatient services. Chin J Hosp Admin. 2003;19:437.
21. Winterkorn JM, Beckman RL. Recovery from ocular ischemic syndrome after treatment with verapamil. J Neuroophthalmol. 1995;15:209–11.
22. Kozobolis VP, Detorakis ET, Georgiadis GS, et al. Perimetric and retrobulbar blood flow changes following carotid endarterectomy. Graefes Arch Clin Exp Ophthalmol. 2007;245:1639–45.
23. Gross R. Neovascular glaucoma and ocular ischemic syndrome. J Glaucoma. 2000;9:409–12.
24. Sivak-Callcott JA, O'Day DM, Gass JD, et al. Evidence based recommendations for the diagnosis and treatment of neovascular glaucoma. Ophthalmology. 2001;108:1767–76.
25. Zhao L, Wang YL. Establishment and application of access database of chronic diseases. J Trad Chin Ophthalmol. 2010;20:241–3.

Part VI

Internal Medicine and Eye Disease

Helicobacter pylori Infection and Glaucoma

23

Dongmei Qian

23.1 Introduction

Helicobacter pylori (HP) is a microaerophilic gram-negative helicobacter that parasitizes between the surface of gastric mucosa and the mucus layer and contains several virulence factors. Glaucoma is a characteristic group of optic neuropathies with elevated intraocular pressure as the main risk factor. It is in essence the apoptosis of retinal ganglion cells. HP and glaucoma belong to two different systems. In the past, ophthalmologists regarded the gastrointestinal diseases, as far as they are concerned, as a stress reaction that only occurs during the period of rapid IOP elevation in glaucoma. And physicians usually regard the acute angle-closure glaucoma as a candidate condition for differential diagnosis for the symptom of internal medical acute pain. However, if we try to understand the two conditions from the perspective of holistic integrative medicine, we will find that HP is a microaerobe whose antigenicity and invasiveness will lead to complex pathological immune responses in multiple sites, while the apoptosis of retinal ganglion cells in glaucoma, on the other hand, requires the participation of autoimmune system. Combining with the latest research progress of sub-specialty, we can find that two seemingly unrelated diseases have common characteristics at different levels: (1) association of pathogenesis based on molecular cytobiology; (3) Immunological correlation in case-control trials; (4) association between radical treatment of HP and glaucoma visual impairment in clinical trials; (5) they are both psychosomatic diseases. Though it is still unclear whether the correlation is concomitant or causal due to limited current understanding of them, their mysterious correlation is going to be revealed in the near future with the development and integration of various subspecialties.

Integrative medicine is based on the whole of human beings. It makes use of the latest medical knowledge, discards the dross, selects the essentials, and combines the most suitable diagnostic techniques to better serve the patients. HIM is an innovation and revolution against the traditional medicine. It represents a new stage in the development of medicine, from specialization to integration. HIM integrates not only all known biological factors, but also other psychological and environmental factors; it requires to integrate both the most advanced findings in all current medicine related fields and the most effective clinical experiences in all medicine-related subspecialties. It can be said that the discussion of the relationship between *Helicobacter pylori* and glaucoma is an interpretation of HIM.

23.2 *Helicobacter pylori*

The Nobel Prize in Physiology or Medicine 2005 was awarded to the Australian doctors Marshall (Department of Gastric and Intestine) and Warren (Department of Pathology) for their discovery and further identification of *Helicobacter pylori* and its function in gastritis and peptic ulcer. They revealed the relation between the *Helicobacter pylori* and chronic gastritis and peptic ulcer, which totally overthrew the concept of "no acid, no ulcer." We are now able to cure the once recurring ulcer to some extent. It is proved clinically that after the eradication of HP, the incidence of recurrence of ulcer decreased dramatically, along with a dramatic decrease of the incidence of other common complications of ulcer such as bleeding, perforation, and pyloric obstruction.

Helicobacter pylori (HP) is a microaerophilic gram-negative helicobacter that parasitizes between the surface of gastric mucosa and the mucus layer and contains various virulence factors, including the two main virulence factors of CagA and VacA; urease, motility, heat-shock

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_23

protein, and adhesin also participate in the pathogenic process. There occurred reports on the relationship between HP infection and gastrointestinal disease around 2000, including reports on the correlation between HP and glaucoma.

23.3 HP Infection and Glaucoma

Glaucoma is the second leading cause of global irreversible blindness. Studies on the pathogenesis, early diagnosis, and effective treatment have been hot topics of ophthalmic research.

Glaucomatous blindness is often associated with elevated intraocular pressure. When the intraocular pressure surpasses the limit of endurance of ocular tissues, especially the retina and optic nerve, vision function will be damaged, which is characterized by pathological high intraocular pressure, optic atrophy, visual field defect, vision loss, etc. The target cells are retinal ganglion cells. The irreversible optic neuropathy is caused by multiple factors. Currently, a number of scholars have concluded that HP infection might be associated with the pathogenesis of glaucoma, using different methods [1–8].

In their joint research, Christos Zavos, Jannis Kountouras and other scholars pointed out that *Helicobacter pylori* was detected in 5 of 43 HP-positive primary open-angle glaucoma patients' aqueous humor and iris specimens, but not in other patients. The possible explanations for the fact that HP was found only in five patients instead of all patients might be the following: (1) the limited amount of samples from the eye or through trabeculectomy leads to absence of HP in the samples and (2) the standard aseptic techniques used before surgery lead to the loss of HP.

23.3.1 HP Test

There are two common HP tests: one is to assess the expression of *Helicobacter pylori*-specific immunoglobulin antibody G (Hp CagA–IgG) in serum and/or in aqueous humor; the other is to do a Carbon 13/14 urea expiratory test for *Helicobacter pylori* current infection and then confirmation by gastric mucosa pathology test through gastroscope.

Jannis Kountourasis et al. reported the measured concentrations of HP-IgG in serum and aqueous in different groups. Serum concentrations are as follows: primary open-angle glaucoma group (69.96 ± 9.69) U/mL, closed-angle glaucoma group (81.37 ± 10.62) U/mL, and control group (44.16 ± 6.48) U/mL; aqueous humor concentrations are as follows: primary open-angle glaucoma group (14.27 ± 3.86) U/mL, closed-angle glaucoma group (14.25 ± 3.39) U/mL, and control group (4.67 ± 1.07) U/mL, and statistical significances were found in all groups. But no significance was found of the IgG concentrations in the primary open-angle glaucoma group and closed-angle glaucoma group. They concluded that the serum and aqueous humor concentration of HP-IgG in primary open-angle glaucoma patients and closed-angle glaucoma patients was higher than in the control group, which supported the connection between HP and glaucoma [3].

23.3.2 The Connection Between Different Types of Glaucoma and HP

The types of glaucoma associated with *Helicobacter pylori* infection in literature reports include primary open-angle glaucoma and normal-tension glaucoma [6, 9]. Most scholars believe that HP infection is associated with primary open-angle glaucoma [1, 4, 8, 10–15], and similar results also come from different regions [16].

23.3.3 The Influence of HP Eradication Therapy on Glaucoma

After HP eradication therapy in the experimental group, Jannis Kountouras and Nikolaos Mylopoulos et al. found that mean IOP and visual field improved significantly in about 83% of the glaucomatous patients, while no significant improvement was found in the control group.

23.3.4 The Possible Pathogenesis of HP-Caused Glaucoma

Based on the correlation studies of HP infection and glaucoma, the possible pathogenesis of glaucoma caused by HP infection is as follows:

1. HP infection promotes platelet-leukocyte aggregation and release of proinflammatory factors like IL-1, 6, 8, 10, 12, TNF-a, and interferon-g and vascular active substances, which destroy the blood-cerebrospinal fluid barrier and aqueous humor circulation, resulting in neuropathies including glaucoma [12].
2. HP infection stimulates monocytes, and activates fibrinogen into fibrin [6, 17].
3. HP infection induces oxidative stress and lipid peroxidation. The oxidative damage to trabecular meshwork and optic nerve may cause glaucoma [12].
4. HP induces irregular humoral response and cellular immune response and has the same molecular mimicry and cross response as neural tissues, which causes dam-

age to neural tissues, leading to neural degenerative diseases including glaucoma [6].

5. HP indirectly affects the nervous system through the release of TNF-a in distance. TNF-a participates in the destruction of the blood-brain barrier through upregulating the expression of matrix metalloproteinase. The leaked HP-specific antibody may get into the aqueous humor circulation to destroy the retinal cells and get involved in the progress of glaucoma [17].
6. As a result of autophagy defect, HP-infected cells can pass the destructed blood-brain barrier and blood-ocular barrier and cause HP self-copying in the autologous vesicles, which may cause glaucomatous neuropathy [2].
7. HP-VacA can promote bacteria survival in cells and regulate the host immune response [18].
8. Mouth is a permanent habitat for HP. HP can reach the eye through the nose, causing ocular disorders, including glaucoma [1, 19].
9. HP infection and glaucoma share the Fas/FasL and mitochondria-mediated apoptosis pathway. There is a cross-reaction between HP antibody and antigen of ciliary epithelium, so it can cause degenerative optic neuropathy by mediating apoptosis by mechanisms like autoimmune which then influences the development and progress of glaucomatous neuropathy [5].
10. Studies have shown that in the iris, the NO released by HP infection is an effective neurotoxin, which would cause apoptosis of retinal ganglion cells in glaucoma. Jannis Kountouras, Christos Zavos, and others showed that the apoptosis of retina cells is alleviated after the induction of NOS by selective anticatalysts or neutralization of TNF-a antibodies, suggesting that suppression of TNF-a or inducible NOS2 isoforms may provide a therapeutic target for neuroprotection in primary open-angle glaucoma [13].
11. HP-produced carcinogenic factors Ki-67, p-53, Bcl-2, and T lymphocytes are involved in cell proliferation and apoptosis. Christos Zavos, Jannis Kountouras, and others found in a study that p-53 was positive in 31.25% of HP-infected persons and it was negative in patients without infection; Bcl-2 was positive in 68.75% of HP-infected patients, and only one case without infection was positive; overexpressions of Ki-67, Bcl-2, and p-53 in HP-infected patients were 19%, 25%, and 37.5%, and no excessive expression was found in patients without infection; T lymphocyte was positive in 100% of infected patients, only one was positive in the noninfected patients, and only one of the HP-infected person was B-cell positive [19].
12. HP-related HSP activates the autoimmune mechanisms, leading to autoimmune disorders and a variety of diseases including glaucoma. Jannis Kountouras and Christos Zavos et al. found that the protective autologous HSP-27 could be modified into HSP-27 by antibodies. The apoptosis of retinal ganglion cells could be induced by purified anti-NSE antibody, which provides a basic immune mechanism-based apoptosis regulation mechanism for glaucoma. Gulgun Tezel, Martin B. Wax, and other scholars also described a mechanism, in which the exogenous Hsp-27 antibody entered human retinal cells by endocytosis, and resulted in apoptotic cell death by morphological change, DNA cleavage, caspase activation, etc. [19].
13. Ghrelin is closely related to HP infection and can pass the blood-eye barrier and affect the ghrelin level in the aqueous humor. It is a kind of peptide and endogenous growth hormone. It has endocrine and paracrine functions and can affect the central nervous system of the pituitary gland and lower thalamus by stimulating the release of growth hormone. It is also involved in metabolism and energy balance and plays a role in the immune system and musculoskeletal system, affecting cell proliferation and identification, gastrointestinal motility, and cardiovascular function. Andreas Katsanos and others believed that, though the function of ghrelin in visual system was not clear, ghrelin was found to have relaxant effect on iris smooth muscle in an animal model, and the existence of ghrelin-mRNA was confirmed in mouse eye. Their research groups also reported that there was no statistical difference between serum ghrelin levels in primary open-angle glaucoma patients and patients in control group, though it was higher in the POAG group; the level of ghrelin in the aqueous humor in primary open-angle glaucoma patients was significantly lower than in the control group; the ratio of serum ghrelin over aqueous ghrelin in primary open-angle glaucoma patients was significantly higher than in the control group, indicating a higher ghrelin level in glaucoma patients [15].

23.4 Conclusion

Research showed that HP infection is one of the causes of glaucoma, especially primary open-angle glaucoma. After the eradication of HP in HP-positive glaucoma patients, the intraocular pressure and visual field results improved significantly compared with the control group, which also indicated the close relationship between glaucoma and HP infection. Further studies with more glaucoma patients are needed to answer the question whether the existence of HP will influence the process of glaucoma, as well as to explore its pathology, in order to better guide glaucoma management.

References

1. Kountouras J, Zavos C. Helicobacter pylori infection as a risk factor for both primary open-angle glaucoma and pseudoexfoliative glaucoma in Thessaloniki Eye Study. Am J Ophthalmol. 2011;152:1079–80.
2. Kountouras J, Zavos C, Deretzi G, et al. Neuroprotection in glaucoma: is there a future role of Helicobacter pylori eradication? Exp Eye Res. 2011;92:436–8.
3. Kountouras J, Mylopoulos N, Boura P, et al. Relationship between Helicobacter pylori infection and glaucoma. Ophthalmology. 2001;108(3):599–604.
4. Peter HG, Simon JW, Muhammad GM, et al. Helicobacter pylori infection and the risk for open-angle glaucoma. Ophthalmology. 2003;110(5):922–5.
5. Jannis K, Christos Z, Dimitrios C. Induction of apoptosis as a proposed pathophysiological link between glaucoma and Helicobacter pylori infection. Med Hypotheses. 2007;68(1):91–3.
6. Jannis K, Christos Z, Emmanuel G, et al. Normal-tension glaucoma and Alzheimer's disease: Helicobacter pylori as a possible common underlying risk factor. Med Hypotheses. 2007;68(1):228–9.
7. Izzotti A, Saccà SC, Bagnis A, Recupero SM. Glaucoma and Helicobacter pylori infection: correlations and controversies. Br J Ophthalmol. 2009;93:1420–7.
8. Peng B, Wang ML, Zhang QF, et al. The relationship between Helicobacter pylori infection and primary open-angle glaucoma. J Bethune Milit Med Coll. 2012;10(6):459–61.
9. Kim JM, Kim SH, Park KH, Han SY, Shim HS. Investigation of the association between Helicobacter pylori infection and normal tension glaucoma. Invest Ophthalmol Vis Sci. 2011;52(2):665–8.
10. Christos Z, Jannis K, Panagiotis K, et al. Modern industrialisation may increase primary open-angle glaucoma prevalence through easier transmission of Helicobacter pylori infection. Med Hypotheses. 2011;76(5):766–7.
11. Angelo Z, Lorenzo R, Cesare H, et al. Glaucoma and Helicobacter pylori: eyes wide shut? Dig Liver Dis. 2012;44:627–8.
12. Bagnis A, Izzotti A, Saccà SC. Helicobacter pylori, oxidative stress and glaucoma. Dig Liver Dis. 2012;44:962–3.
13. Zavos C, Kountouras J, Sakkias G, Venizelos I, Deretzi G, Arapoglou S. Histological presence of Helicobacter pylori bacteria in the trabeculum and iris of patients with primary open-angle glaucoma. Ophthalmic Res. 2012;47:150–6.
14. Kountouras J, Mylopoulos N, Chatzopoulos D, Boura P, Konstas AG, Venizelo J. Eradication of Helicobacter pylori may be beneficial in the management of chronic open-angle glaucoma. Arch Intern Med. 2002;162(11):1237–44.
15. Katsanos A, Dastiridou A, Georgoulia P, Cholevas P, Kotoula M, Tsironi EE. Plasma and aqueous humour levels of ghrelin in open-angle glaucoma patients. Clin Exp Ophthalmol. 2011;39:324–9.
16. Kountouras J, Zavos C, Katsinelos P, Grigoriadis N, Deretzi G, Tzilves D. Greek and Israeli patterns of Helicobacter pylori infection and their association with glaucoma: similarities or diversities? J Glaucoma. 2008;17(6):503–4.
17. Christos Z, Jannis K, Lemonia S, et al. Mitogen-activated protein kinase (MAPK) intracellular signalling in the aqueous humour activated by Helicobacter pylori may have a role in glaucoma. Med Hypotheses. 2007;68(4):928–9.
18. Zavos C, Kountouras J. Increased levels of Helicobacter pylori IgG antibodies in aqueos humor of patients with primary open angle and exfoliation glaucoma. Arch Ophthalmol. 2003;241(11):884–90.
19. Tezel G, Wax MB. The mechanisms of hsp27 antibody-mediated apoptosis in retinal neuronal cells. J Neurosci. 2000;20(10):3552–62.

Diabetes and Diabetic Eye Disease

24

Ye Zhang, Ningli Wang, and Xiao Zhang

24.1 Introduction

As we all know, diabetes can lead to diabetic eye diseases. At present, we have detailed understanding of many treatment measures for eye diseases caused by diabetes. The downside is that ophthalmologists lack an overall understanding of diabetes, and this limitation puts us in a passive state in the prevention and treatment of diabetic eye diseases. When thinking from the perspective of integrative medicine, we will find a lot of problems that need to be demonstrated and elaborated systematically: For example, why do some people suffer from severe eye diseases while others have healthy eyes with the same level of diabetes control? What kind of eye diseases are directly related to diabetes? What is the exact pathogenesis of diabetic retinopathy? What is the relationship between diabetic eye diseases and other complications of diabetes, such as diabetic nephropathy? Only when we are aware of the existence of these problems and through analyzing these problems using the theory of integrative medicine and through integrating the advanced theories and advanced technologies of all relevant disciplines are we likely to have a comprehensive understanding of diabetic eye diseases, properly prevent the situations where interventions are made only when diabetic eye diseases have occurred from happening, be able to tell the diseases of the whole body of a patient through ocular manifestations, change our passive state to an active state and change our localized view to a view in the prevention and treatment of diabetic eye diseases, and achieve early intervention and effective treatment of diabetic retinopathy in clinical practice in order to reduce the rate of blindness.

With the socioeconomic development and changes in people's lifestyles, diabetes mellitus has evolved from a disease that mainly occurs in the population of developed countries to an epidemic disease affecting global public health. Diabetes is a complex multifactorial and multisystem disease, and is associated with a variety of chronic complications including diabetic eye diseases, especially diabetic retinopathy (DR), which is one of the most common complications of diabetes and is currently the leading cause of blindness in the world.

24.2 Introduction on Diabetes

In 1999, the World Health Organization (WHO) defined diabetes as "a state of relative or absolute deficiency of insulin secretion, characterized by risks of hyperglycemia, microvascular and macrovascular complications" [1]. Diabetes can be divided into type 1 (insulin deficiency) and type 2 (insulin resistance).

Diabetes is a global epidemic. It is estimated that in 2005 the number of world's diabetes patients is nearly 200 million [1]. Change of dietary structure and lack of exercise will result in an increase of prevalence rate of diabetes in the future. It is estimated that by 2025, about 300 million people around the world will suffer from diabetes [2]. And most of the world's new diabetes cases appear in developing countries. Data from WHO estimated that there are 52.4 million diabetes patients in Asia [3], and will increase sharply in the next 25 years to about 121.8 million [4].

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_24

The chronic complications of diabetes include macrovascular complications, such as arteriosclerosis, coronary atherosclerotic heart disease, stroke, and peripheral vascular diseases, as well as microvascular complications, such as peripheral and autonomic neuropathy, renal insufficiency or failure, and DR. Diabetic eye disease is one of the most common complications of diabetes, and can be divided into DR and non-retinal eye complications.

24.3 Diabetic Retinopathy

DR is a common complication of diabetes, and about 1/3 of diabetic patients have varying degrees of DR. It is the main cause of blindness in people of 20–74 years of age, and the morbidity and blindness rate is increasing year by year [5, 6]. The incidence and progression of DR are associated with a variety of factors, and common risk factors include the duration of diabetes mellitus, level of blood glucose control, hypertension, kidney disease, etc. In patients with more than 20 years of diabetes, almost all patients with type 1 diabetes and more than 60% of patients with type 2 diabetes will develop a certain degree of retinopathy [1]. Early diagnosis and active treatment are critical to preventing or delaying its progression [1].

24.3.1 Pathological Changes and Pathogenesis

The mechanism of histopathological changes caused by diabetes is complex, and it may be secondary to metabolic abnormalities caused by chronic hyperglycemia. Intraventricular changes include microvascular wall basement membrane thickening, pericyte reduction, microaneurysm formation, hemorrhage, cotton-wool spot, exudate, abnormal changes in vascular diameter, and intraretinal microvascular abnormalities (IRMA) [1]. The formation of neovascularization is another manifestation, and these abnormal blood vessels can be formed in the optic nerve or retinal surface, leading to retinal hemorrhage, vitreous traction, macular deformation, and retinal detachment [1].

24.3.2 Clinical Manifestations

24.3.2.1 Fundus Manifestations

According to the severity of the lesion, DR is divided into nonproliferative diabetic retinopathy (NPDR) or background diabetic retinopathy (BDR) and proliferative diabetic retinopathy (PDR). Fundus manifestations of NPDR include retinal vein dilatation, microaneurysm, deep and superficial hemorrhage, hard exudate, cotton-wool spot, and retinal edema (macular edema); PDR is when the lesion further aggravates, large areas of capillary occlusion and retinal neovascularization occur, and then the new blood vessels grow from the surface of the retina into the space between inner limiting membrane and posterior limiting membrane of vitreous, forming fibrous vascular membrane. Neovascularizations are easily to rupture with a large amount of vitreous blood, and ultimately lead to retinal detachment. The international clinical diabetic retinopathy severity grading is shown in Table 24.1 [7–9].

Diabetic macular edema (DME) can occur at any of the above stages, and the international DME severity grading is shown in Table 24.2 [7, 10].

Table 24.1 The international clinical diabetic retinopathy severity grading

Suggested lesion severity	Funduscopic findings after pupillary dilation
No obvious retinopathy	Normal
Mild NPDR	Only microaneurysms
Moderate NPDR	Lesions are between mild and severe NPDR
Severe NPDR	Any of the following (the 4-2-1 rule): – Each of the four quadrants has more than 20 intraretinal bleeding points – Two quadrants have definite retinal venous beading – One quadrant presents definite IRMA In addition, there is no PDR manifestation
PDR	One of the following: – Neovascularization (iris, angle of anterior chamber, optic disc, or other location) – Vitreous hemorrhage or preretinal hemorrhage

Note: *NPDR* non-proliferative diabetic retinopathy, *IRMA* retinal microvascular abnormalities, *PDR* proliferative diabetic retinopathy

Table 24.2 The international clinical diabetic macular edema severity grading

Suggested lesion severity	Funduscopic findings after pupillary dilation
DME definitely absent	The posterior pole of the fundus is with no significant retinal thickening or hard exudation
DME definitely present	The posterior pole of the fundus is with significant retinal thickening or hard exudation
If DME exists, it can be classified as follows:	
Suggested lesion severity	Funduscopic findings after pupillary dilation
Mild DME	Retinal thickening and hard exudation are present at the posterior pole and are far from the macular center
Moderate DME	Retinal thickening and hard exudation are close to the macula but not involving the macular center
Severe DME	Retinal thickening and hard exudation involve the macular center

Note: *DME* diabetic macular edema

24.3.2.2 Changes of Visual Function

There may be no symptoms in the early stage of the disease. When the lesions involved the macular and the function of retinal neurons changed, there will be different degrees of vision loss.

24.3.3 Diagnosis

1. History of diabetes mellitus.
2. Slit lamp and gonioscope examination: Carefully observe if there is neovascularization on the iris or the angle of anterior chamber.
3. Pharmacologic mydriasis: Use indirect ophthalmoscopy lenses with the slit lamp to exam the retina and find the presence of retinal neovascularization and macular edema. Indirect ophthalmoscopy can be used to check the peripheral retina.
4. Measure fasting blood glucose, glycosylated hemoglobin, and if necessary glucose tolerance, as well as blood pressure.
5. Fundus fluorescein angiography (FFA) examination to determine whether there is abnormal retinal vascular perfusion area, macular ischemia, microaneurysms, IRMA, and so on.
6. Optical coherence tomography (OCT) examination to assess the presence of macular edema and the extent of edema [1, 9, 10].

24.3.4 Treatment

Early diagnosis and timely treatment of DR can effectively reduce visual impairment and blindness. Two milestone studies of diabetic retinopathy, namely Diabetic Retinopathy Study (DRS) and Early Treatment of Diabetic Retinopathy Study (ETDRS), have shown that effective treatment of DR can reduce the loss of vision by 90% [11, 12].

1. Clinically significant macular edemas

   Clinically significant macular edemas need treatment, including macular focal or grid photocoagulation. Diagnostic criteria are any of the following: (a) retinal thickening within 500 μm of the macular fovea; (b) hard exudate within 500 μm of the macular fovea, causing adjacent retinal thickening; and (c) retinal thickening is greater than one disc area, and partly in the area of one disc area centered at the macular fovea [1, 9]. For patients with extensive macular edema, isolated edema under macular center, or macular edema with fovea ischemia or patients for whom photocoagulation produced poor efficacy, intravitreal injection of anti-VEGF drugs or corticosteroid drugs, or intravitreal injection combined with photocoagulation, may be effective [1, 9].
2. Proliferative diabetic retinopathy

   In any of the following circumstances pan-retinal photocoagulation (PRP) treatment should be taken: (a) optic disc neovascularization of 1/4 to 1/3 disc diameter; (b) various degrees of optic disc neovascularization with preretinal hemorrhage or vitreous hemorrhage; (c) retinal neovascularization of greater than 1/2 disc diameter with preretinal hemorrhage or vitreous hemorrhage; and (d) neovascularization of iris or angle of the anterior chamber [1, 9, 10].
3. Vitrectomy

   Vitrectomy should be taken in any of the following conditions: (a) decreased visual acuity caused by dense vitreous hemorrhage, especially when this has lasted for several months; (b) tractional retinal detachment involving the macular area with continuous progression; (c) macular epiretinal membrane formation or newly emerging macular translocation; (d) severe retinal neovascularization and fibrogenesis membrane that is insensitive to photocoagulation; and (e) dense pre-macular hemorrhage [1, 9, 10].

24.3.5 Follow-Up

For diabetes patients without DR, an annual fundus examination after pupillary dilation is advised. The follow-up time for mild NPDR, moderate-to-severe NPDR, and PDR patients should be every 6–9 months, 4–6 months, and 2–3 months, respectively [1, 9, 10].

24.4 Non-retinal Eye Complications

Other histopathological changes caused by diabetes include decreased corneal sensitivity and adhesion of corneal endothelial cells, lens osmotic expansion and cataract formation, choroidal capillary damage, choroidal and ciliary body pigmentary epithelial basement membrane thickening, and iris neovascularization (rubeosis iridis), causing a variety of eye complications other than DR [13–18]

24.4.1 Conjunctiva

Conjunctiva complications include mainly spindle-shaped or cystic dark red spot of microaneurysms, occurring frequently in the palpebral fissure, easily misdiagnosed as subconjunctival hemorrhage. Other manifestations include veins tortuous, cystic dilatation, and uneven blood column, spiral capillary, and slow blood flow of capillaries and small veins with erythrocyte aggregation [10].

24.4.2 Cornea

Diabetic patients may have a significant decrease in corneal sensitivity, and the severity of the decline is usually positively correlated with the severity of DR [19]. It is reported that dry eye is associated with diabetes, and the severity of dry eye is positively correlated with the severity of DR [20]. In addition, the incidence of contact lens-associated bacterial keratitis and neuropathic corneal ulcer in diabetic patients is high [21, 22]. Diabetic patients are prone to have recurrent corneal erosion, especially after photocoagulation or vitreous surgery [23].

24.4.3 Iris

1. Iridocyclitis: Body immunity is declined in patients with diabetes mellitus, so they are susceptible to infection. Meanwhile, the blood-aqueous barrier is damaged and vascular permeability increased, causing plasma component outflow to the anterior chamber, leading to iridocyclitis [24].
2. Iris neovascularization: Incidence rate of iris neovascularization in diabetic patients is 1–17%, and the number can be up to 65% in PDR patients [25–27]. Extensive retinal ischemia induces the production of vascular endothelial growth factor that stimulates iris and anterior chamber angle neovascularization, manifesting as irregular tiny winding new vessels on the surface of iris, especially the pupil margin, also known as rubeosis iridis [8, 10].

24.4.4 Lens

1. Refractive changes: When the blood glucose elevates and the content of inorganic salt in blood decreases, the aqueous osmotic pressure will drop and the aqueous humor will infiltrate into the lens, causing diopter change of the lens and leading to myopia. When the blood glucose decreases and the aqueous osmotic pressure increases, water flows out from the lens, leading to relative hyperopia. These short-term rapid changes are characteristics of diopter changes of lens caused by diabetes, and the change can be as high as 3–4 diopters [10].
2. Cataract: The risk of cataract in diabetes patients is about 2–4 times higher than nondiabetic individuals [28, 29]. In diabetic patients with elevated blood glucose, more glucose will enter the lens. The aldose reductase will then be activated, leading to sorbitol accumulation in the lens. The intracellular osmotic pressure will increase as a result, making lens fiber absorb water and swell, which is followed by lens degeneration and turbidity, and finally the occurrence of cataract. Cataract in diabetes patients can be divided into two types, including true diabetic cataract and age-related cortical cataract. The former type is typically seen in young patients with diabetes (type 1 diabetes), manifesting as milky white snowflake-like opaque under the anterior capsule of the lens and progressing rapidly. The latter type usually has no obvious difference with age-related cataract, but can occur 20–30 years in advance compared with nondiabetic individuals [1, 10].

24.4.5 Glaucoma

Early iris neovascularization manifests as small blood vessels clustering at pupil margin. When these blood vessels grow across the iris surface, fibrous tissue contraction often occurs concomitantly, leading to trabecular meshwork traction and adhesion. Meanwhile, neovascularization of the anterior chamber angle can block the trabecular meshwork, resulting in neovascular glaucoma [1, 10]. Although PRP is extensively used, PDR is still the main cause of neovascular glaucoma [1].

24.4.6 Abnormal Optic Nerve

Incidence rate of optic neuropathy in diabetic patients is high, and the clinical manifestations are various. The more serious DR is, the greater the possibility of occurrence of optic neuropathy is, but the two are not parallel [30]. Optic neuropathy of diabetes can manifest as anterior ischemic optic neuropathy, optic disc edema, acute optic neuritis-like changes, optic disc neovascularization, optic atrophy, etc. [30].

24.4.7 Abnormal Cranial Nerves

Due to local small vascular obstruction associated with ischemic demyelination, isolated cranial nerve palsy can occur in diabetic patients, such as oculomotor nerve, trigeminal nerve, or abducens nerve palsy, manifesting as extraocular muscle movement disorder, diplopia, as well as mydriasis. If the examination shows involvement of more than one cranial nerve, concomitant presence of other neurological signs, gradual worsening of the condition, or failure to achieve full recovery within 3 months, other reasons should be investigated [1, 10].

24.5 Other Issues

24.5.1 Primary Open-Angle Glaucoma

Population-based studies including Baltimore, Barbados, Beaver Dam, and Blue Mountain studies have contradictory

conclusions on the correlation between POAG and diabetes. The former two studies suggested that there was no correlation between diabetes and POAG, while the latter two studies confirmed that POAG was related to diabetes [31–34]. Therefore, the relationship between diabetes and POAG is not conclusive. But when treating POAG patients, attention should be paid to β-adrenergic receptor antagonist, which has the side effects of reducing glucose tolerance and obscuring the signs of hypoglycemia and thus should be used cautiously in diabetic patients [1].

24.5.2 Endophthalmitis

Studies have shown that the risk of postoperative endophthalmitis in diabetic patients is higher than in nondiabetic individuals [35, 36]. A possible reason is that diabetic patients are prone to have wound injury or persistent wound nonunion. In addition, vitreous surgery of PDR complications often needs longer operation time and more equipment replacement through the sclera incision at pars plana, which increases the risk of endophthalmitis [1].

24.6 Summary

The manifestations of diabetic eye diseases are various, among which DR is one of the important causes of blindness in China. Early diagnosis, early prevention, and treatment play an important role in the control of visual disability caused by DR. Although currently there are effective treatment measures for DR, there are still obstacles in the timely treatment and management of diabetic patients. The reasons include the fact that some patients with diabetes are not aware of the importance of fundus examination; some patients cannot return for follow-up regularly because of financial or distance problems; and there is lack of communication and coordination between systematic treatment and ophthalmic treatment. Our medical workers need to further improve the screening of DR in the community, strengthen the education of diabetic patients, and promote communication between physicians, general practitioners, and ophthalmologists, in order to work together to reduce the incidence rate of blindness in diabetic patients.

References

1. Scott IU, Flynn HW, Smiddy WE. Diabetes and ocular disease: past, present, and future therapies. Translated by Liu NP, Liu XP. Beijing: People's Medical Publishing House; 2014.
2. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care. 1995;21:1414–31.
3. World Health Organization. World Diabetes Day 2005, Nov 11, 2005.
4. Sarah W, Gojka R, Anders G, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047–53.
5. Li L, Zou DJ. Diabetic eye diseases. J Clin Intern Med. 2010;27:151–4.
6. Li XX. Strategies for prevention and treatment of diabetic retinopathy. Chin J Ophthalmol. 2008;44:6–8.
7. Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110:1677–82.
8. Hui YN, Chen JQ, Chen XM, et al. Ophthalmology. Beijing: People's Medical Publishing House; 2004. p. 240.
9. Wei WB, et al. The wills eye manual. Beijing: Science Press; 2014. p. 447–53.
10. Ge J, Zhao JL, Cui H, et al. Ophthalmology, vol. 221. Beijing: People's Medical Publishing House; 2005. p. 304–305, 430.
11. American Academy of Ophthalmology. Diabetic retinopathy preferred practice pattern. San Francisco, CA: American Academy of Ophthalmology; 2008.
12. Diabetic Retinopathy Study Research Group. A modification of the Airlie House classification of diabetic retinopathy. Report 7. Invest Ophthalmol Vis Sci. 1981;21:210–26.
13. Kinoshita JH. Mechanisms initiating cataract formation, proctor lecture. Investig Ophthalmol. 1974;13:713–24.
14. Harry J, Mission G. Clinical ophthalmic pathology: principles of diseases of the eye and associated structure. London: Butterworth-Heinemann; 2001. p. 282–7.
15. Keoleian GM, Pach JM, Hodge DO. Structural and functional studies of the corneal endothelium in diabetes mellitus. Am J Ophthalmol. 1992;113:64–70.
16. Hidayat AA, Fine BS. Diabetic choroidopathy light and electron microscopic observations of seven cases. Ophthalmology. 1985;92:512–22.
17. Fisher RF. Factors which influence the thickness of basement membrane in diabetes: evidence of humoral control. Trans Ophthalmol Soc UK. 1979;99:10–21.
18. Wendel RT, Patel AC, Kelly NE, et al. Vitreous surgery for macular holes [see comment]. Ophthalmology. 1993;100:1671–6.
19. Saito J, Enoki M, Hara M, et al. Correlation of corneal sensation, but not of basal or reflex tear secretion, with the stage of diabetic retinopathy. Cornea. 2003;22:15–8.
20. Nepp J, Abela C, Polzer I, et al. Is there a correlation between the severity of diabetic retinopathy and keratoconjunctivitis sicca? Cornea. 2000;19:487–91.
21. Eichenbaum JW, Feldstein M, Podos SM. Extended-wear soft contact lenses and corneal ulcers. Br J Ophthalmol. 1982;66:663–6.
22. Hyndiuk RA, Kazarian EL, Schultz RO, et al. Neurotrophic corneal ulcers in diabetes mellitus. Arch Ophthalmol. 1977;95:2193–6.
23. Arentsen J, Tasman W. Using a bandage contact lens to prevent recurrent corneal erosion during photocoagulation in patients with diabetes. Am J Ophthalmol. 1981;92:714–6.
24. Jiang GY. Practical diabetology. Beijing: People's Medical Publishing House; 1992. p. 228.
25. Armaly MF, Baloglou PJ. Diabetes mellitus and the eye, I: changes in the anterior segment. Arch Ophthalmol. 1967;77:485–92.
26. Madsen PH. Haemorrhagic glaucoma: comparative study in diabetic and nondiabetic patients. Br J Ophthalmol. 1971;55:444–50.
27. Ohrt V. The frequency of rubeosis iridis in diabetic patients. Acta Ophthalmol. 1971;49:301–7.
28. Klein BE, Klein R, Moss SE. Prevalence of cataracts in a population-based study of persons with diabetes mellitus. Ophthalmology. 1985;92:1191–6.

29. Rowe NG, Mitchell PG, Cumming RG, et al. Diabetes, fasting blood glucose and age-related cataract: the Blue Mountains Eye Study. Ophthalmic Epidemiol. 2000;7:103–14.
30. Ding XY, Ou JX, Ma HJ, et al. A clinical analysis of diabetic optic neuropathy. Chin J Pract Ophthalmol. 2005;23:1269–74.
31. Tielsch JM, Katz J, Quigley HA, et al. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. Ophthalmology. 1995;102:48–53.
32. Leske MC, Connell AM, Wu SY, et al. Risk factors for open-angle glaucoma. The Barbados Eye Study. Arch Ophthalmol. 1995;113:918–24.
33. Klein BE, Klein R, Jensen SC. Open-angle glaucoma and older-onset diabetes: the Beaver Dam Eye Study. Ophthalmology. 1994;101:1173–7.
34. Mitchell P, Smith W, Chey T, et al. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study. Aust Ophthalmol. 1997;104:712–8.
35. Philips WB II, Tasman WS. Postoperative endophthalmitis in association with diabetes mellitus. Ophthalmology. 1994;101:508–18.
36. Lehmann OJ, Bunce C, Matheson MM, et al. Risk factors for development of post-trabeculectomy endophthalmitis. Br J Ophthalmol. 2000;84:1349–53.

Diabetic Retinopathy in the Eyes of Endocrine Doctors

25

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25.1 Introduction

Diabetic retinopathy is the most common eye complication of diabetes and one of the major causes of human blindness. The main causes of visual impairment are diabetic macular edema and proliferative diabetic retinopathy. From the perspective of endocrinologists, for patients with diabetic retinopathy, systemic treatments, including the control of blood glucose and blood lipids, are equally important as local treatment for the treatment of lesions that have occurred and prevention of visual impairment from occurring. Patients who need early intervention in diabetic retinopathy patients should be retained in the endocrinology department, and high-risk patients should be referred to the ophthalmology department, particularly those who need to be diagnosed and screened for severe non-proliferative retinopathy. This is a key issue to be solved. Through integration of the latest advances in epidemiological studies and clinical experiences, regular diabetic retinopathy screening, and intervention against risk factors, it is possible to prevent the occurrence of diabetic retinopathy. This chapter can help us understand how endocrinology and ophthalmology should work together to achieve the goal that the patients who need early intervention (not yet with diabetic retinopathy) stay in the endocrinology department for control of blood sugar, while high-risk patients (with diabetic retinopathy that may impact visual acuity) are referred to the ophthalmology department. Let's work together to improve the quality of life of patients by preventing or reducing the occurrence of visual impairment.

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25.2 The Prevalence of Diabetic Retinopathy

With the change of lifestyle and the aging of the population, diabetes is rapidly becoming more and more popular in the world, and the number of patients with diabetic retinopathy has increased year by year as a result. Diabetic retinopathy is an important microvascular complication of diabetes and is the leading cause of visual impairment in adults aged 20–74 [1]. Recent epidemiological data show that there are more than 93 million people with diabetic retinopathy in the world, and 28 million patients are at risk of visual impairment, especially the 17 million patients with proliferative diabetic retinopathy [2]. Based on the study of natural population, the total prevalence of retinopathy in diabetic patients was 43.1%. Among them, the prevalence of retinopathy in patients with diabetes mellitus was 65.2% and that of newly diagnosed diabetic patients was 33.5% [3].

The main cause of visual impairment in diabetic retinopathy is diabetic macular edema and proliferative diabetic retinopathy; macular edema can occur at any stage of diabetic retinopathy, and the incidence of macular edema increases as diabetic retinopathy worsens. The incidence of macular edema is less than 10% in mild non-proliferative diabetic retinopathy patients and about 70% in severe proliferative diabetic retinopathy patients.

There are certain racial differences in diabetic retinopathy. At present, epidemiological research data about diabetic retinopathy and macular lesions in China based on the natural populations is very limited.

Our study found that the prevalence of retinopathy in Chinese may be relatively low, while the prevalence of diabetic macular edema is relatively high. The prevalence of retinopathy in diabetic patients was only 9.9%, while the prevalence of diabetic macular edema is as high as 8.8%. Given the fact that the prevalence of diabetes in China's adults is 10%, diabetic retinopathy and macular edema will be important vision-threatening factors [4].

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_25

25.3 The Main Influencing Factors of Diabetic Retinopathy

To prevent and treat diabetic retinopathy, the first is to identify the risk factors for diabetic retinopathy and its pathogenesis, and then take timely intervention. At present, among the known risk factors for diabetic retinopathy, in addition to genetic factors, diabetes course and blood glucose levels are recognized as the main risk factors.

The prevalence of retinopathy in patients with diabetes mellitus for less than 5 years was 17% for type 1 diabetes mellitus and 29% for type 2 diabetes, and the prevalence in patients with diabetes mellitus for more than 15 years was close to 100% for type 1 diabetes and 78% for type 2 diabetes [5, 6]. However, it should be noted that the incidence of non-proliferative retinopathy was exponentially increased, while its progression to proliferative retinopathy increased steadily.

Blood glucose control can prevent or reduce the occurrence and development of retinopathy. For type 1 diabetes, the Diabetes Control and Complications Study (DCCT) results showed an average reduction in the incidence of diabetic retinopathy by 76% in the intensive treatment group compared with the conventional treatment group (glycosylated hemoglobin HbA1 was about 2% lower in the former), and the diabetic retina disease progression slowed by 54%. At the end of the DCCT study, although the initial intensive treatment group and the conventional treatment group were at the same level of glycemic control (HbA1c) levels (8 years later, the intensive treatment group was 7.98%; conventional treatment group 8.07%), the treatment regimen still had a lasting "memory" effect on the patient, and the incidence of further progression of diabetic retinopathy in the intensive treatment group was significantly lower. The intensive treatment group experienced a 50% reduction in severe retinal outcome initially. The price of using blood glucose control to prevent the occurrence of complications of diabetes, to a certain extent, is making the blood sugar low, and therefore hypoglycemia should also be watched. For type 2 diabetes, the research findings are similar to those in DCCT. Epidemiological analysis of UK Prospective Diabetes Study (UKPDS) showed that the risk of retinopathy in type 2 diabetic patients was associated with the persistence of hyperglycemia: for every 1% decrease (9–8%) in HbA1c, there is a 35% reduction in retinopathy.

In addition to blood glucose control, blood pressure control is also associated with the occurrence and progression of a number of stages of diabetic retinopathy. Strict control of blood pressure, in a sense, is more obvious than the benefits of lowering blood sugar. The results of UKPDS are as follows: strict blood pressure control group's average blood pressure is 144/82 mmHg, while the non-strict blood pressure control group's blood pressure is 154/87 mmHg. Comparison of the two groups shows that microvascular disease decreased by 37%, fundus deterioration by 37%, and visual deterioration by 47% in the strict blood pressure control group. Epidemiological studies of diabetic retinopathy in Wisconsin show that systolic blood pressure is associated with the development of non-proliferative retinopathy, and diastolic blood pressure is associated with its progression.

Lipid control is also associated with the development and progression of diabetic retinopathy. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that, compared with the placebo group, fenofibrate, as a clinical lipid-lowering drug, reduced the number of cases of diabetic macular edema and proliferative retinopathy that need first laser treatment by 31% and 30%, respectively. But fenofibrate did not reduce the incidence of diabetic retinopathy and macular edema, hard exudation progression, or visual deterioration, and only the progression of the original retinopathy was significantly slowed down [7]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that 4 years' treatment with fenofibrate combined with simvastatin reduced the progression of diabetic retinopathy by 40% type 2 diabetes patients, and this effect is independent of blood glucose control [6]. FIELD study [7] and ACCORD study [8] showed that fenofibrate should be recommended for patients with type 2 diabetes mellitus with diabetic retinopathy, especially those with diabetic macular edema requiring laser photocoagulation, for effective control of progression of diabetic retinopathy.

Diabetes combined with pregnancy can also significantly aggravate the progression of retinopathy, so special emphasis should be placed on prepregnancy, in-pregnancy, as well as post-pregnancy fundus examination.

We found that subclinical hypothyroidism is also a risk factor for visual retinopathy. Diabetic patients with subclinical hypothyroidism have a fourfold higher risk of retinal lesions. For patients with diabetes, this is a risk factor of retinopathy we can control through interventions and thus worthy of our attention [9].

25.4 Treatment of Diabetic Retinopathy

Visual impairment in diabetic retinopathy is difficult to reverse once it occurs. Therefore, the strategy for clinical management of diabetic retinopathy is focused on prevention. The first is to prevent its occurrence; in the event of diabetic retinopathy, it is important to inhibit the progression into severe macular edema or proliferative diabetic retinopathy and to timely implement reasonable treatment and intervention to reduce visual impairment and reduce the rate of blindness.

The current treatment of diabetic retinopathy includes drugs and surgery. It should be diagnosed and classified by ophthalmologist in reference to the 2002 international clinical diabetic retinopathy diagnostic criteria. However, these patients seek treatment mostly due to medical diseases, so how the endocrinology department should cooperate with the ophthalmology department to retain those who need early intervention at the endocrinology department and refer the high-risk patients, especially those who need to be diagnosed and screened for severe proliferative retinopathy, to the ophthalmology department based on specific criteria is a key issue that needs to be addressed. Through regular screening for diabetic retinopathy and intervention against risk factors, it is possible to prevent the occurrence of diabetic retinopathy. For mild or moderate non-proliferative retinopathy, medical treatment should be given for risk factor control; and for severe non-proliferative retinopathy or early proliferative retinopathy, photocoagulation treatment should be considered according to the type of diabetes. The Early Treatment Diabetic Retinopathy Study (ETDRS) has demonstrated that patients with type 2 diabetes have a 50% lower risk of severe vision loss and of needing vitrectomy if they receive photocoagulation before developing a high-risk proliferative retinopathy. For type 1 diabetes, even when photocoagulation is performed, the risk of progression into high-risk proliferative retinopathy and severe vision loss and of requiring vitrectomy is not significantly lowered [10]. For macular edema, it now appears that local injection of anti-vascular endothelial growth factor (VEGF) preparations and local application or oral administration of glucocorticoids and other drugs have a certain application prospects. Based on the current understanding of the pathophysiological characteristics of diabetic macular edema, the clinical treatment of macular edema is mainly ophthalmological treatments, including laser photocoagulation, vitreous cavity drug injection, and vitrectomy and other methods, provided that blood glucose and other risk factors are under control.

Although the clinical prevention and treatment of diabetic retinopathy have made significant progress, the incidence of diabetic retinopathy has not decreased significantly. The work to prevent the occurrence of diabetic retinopathy, inhibit the progression of diabetic retinopathy, reduce visual impairment, and reduce blindness rate still faces many challenges. This requires ophthalmology, endocrinology, and other disciplines to collaborate to carry out comprehensive prevention and control.

There is still a long way to go in clinical prevention and treatment of diabetic retinopathy.

References

1. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology. 1998;105(10):1801–15.
2. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556–64.
3. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984;102(4):520–6.
4. Yuan MX, Peng ZH, Xin Z, et al. Low prevalence of diabetic retinopathy in a Chinese population. Diabetes Care. 2012;35(8):e61.
5. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984;102(4):527–32.
6. Wang NL, Wang FH, Liang YB. A survey on the current main eye diseases leading to blindness among the adults of Yongnian County, Hebei Province: a progression report of Handan Eye Diseases Study. J Capital Med Univ. 2010;31(1):11–7.
7. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet. 2007;370:1687–97.
8. ACCORD Study Group, ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363:233–44.
9. Yang JK, Liu W, Shi J, et al. An association between subclinical hypothyroidism and sight-threatening diabetic retinopathy in type 2 diabetic patients. Diabetes Care. 2010;33(5):1018–20.
10. Ferris FL 3rd. How effective are treatments for diabetic retinopathy? JAMA. 1993;269(10):1290–1.

The Chronic Kidney Disease and Abnormal Retinal Blood Vessels

26

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26.1 Introduction

Chronic kidney disease is a condition characterized by a gradual damage of kidney structure and function, irrespective of the underlying causes. The main manifestations are proteinuria, hematuria, edema, and hypertension, with or without renal dysfunction. The retinal vasculature is a unique site where the microcirculation can be noninvasively imaged in vivo, and it belongs to the small blood vessel category and is part of the systemic microcirculation. Most ophthalmologists and nephrologists consider that retinal vasculature monitoring for early diagnosis of chronic kidney disease is not a satisfactory method as yet, because the involvement of diabetes, hypertension, and other systemic diseases and the variability in retinal vascular abnormalities make the relationship between retinal vasculature and chronic kidney disease quite complicated. However, the diversified thinking mode of integrated medicine may provide further insights into the disease and clinical research: (1) Similarities account for the association between different diseases. Both glomerular and retinal blood vessels belong to microcirculation system. This similarity hints that the pathological changes of chronic glomerular disease, diabetic nephropathy, and hypertensive nephropathy may manifest themselves through the fundus tissues which serve as a special window. (2) Differentiation and integration is a unity of opposites, and integration is based on differentiation. There are many indicators of retinal vascular abnormalities, so it raises the following question: Which is the best predictor of kidney disease and renal dysfunction? Only through further breakdown of the indicators can the problems be better specified. Animal experiments have confirmed the association between retinal vascular abnormalities and nephropathy. Epidemiological studies have shown that this association can be repeated in populations of different geographical and ethnic backgrounds, suggesting that the association may be unaffected by environmental or genetic background. (3) Understanding of a disease should focus not only on the association between different factors, but also on the dynamic effects of different factors on the disease. For example, persistently elevated arterial pressure in hypertension can lead to retinal vasculopathy, renal arteriosclerosis, and other target organ damage. Meanwhile, abnormalities in the microcirculation system can also affect the systemic blood pressure, forming a vicious circle. Through following this train of thought, combined with prospective cohort studies, it is possible to achieve individualized predictions of chronic kidney disease by retinal blood vessels in the future.

The retinal vasculature is the only microvascular system that can be observed noninvasively in the human body. In 1823, Johannes Purkinje invented the direct ophthalmoscope. In 1898, Marcus Gunn, the Scottish physician, used the ophthalmoscope for fundus observation and described a series of abnormal changes in retinal vessels in patients with cerebrovascular disease. Since then, retinal vasculature was considered to be one of the indicators that could reflect the microvascular status of the whole body. The status of human microcirculation can be observed by noninvasive retinal microvascular imaging technology. In recent years, with the development of high-resolution fundus photography and digital image analysis techniques, the researchers can evaluate retinal vasculature more accurately and reliably so as to reveal the relationship between the eyes and systemic diseases.

Chronic kidney disease is a common disease which is a serious threat to human health, and its main clinical manifestations are proteinuria, hematuria, edema, and hypertension, with or without renal dysfunction. Chronic kidney disease is characterized by insidious onset, sustained progression, multitudinous complications, high medical costs,

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_26

and high mortality and has diverse etiologies. Glomerular diseases are a leading cause of chronic kidney disease, followed by hypertensive kidney disease and diabetic nephropathy. Hypertension, diabetes, hyperlipidemia, and aging are the major risk factors for the development and progression of chronic kidney disease. Sustained progression of chronic kidney disease can cause irreversible loss of nephron and renal function, leading to chronic renal failure characterized by metabolite retention, electrolyte disturbance, acid-base imbalance, and endocrine dyscrasia, ultimately resulting in end-stage renal disease (ESRD) and uremia. The National Kidney Foundation has divided chronic kidney disease into five stages according to the glomerular filtration rate (GFR): stage 1 GFR ≥90 mL/min/1.73 m^2; stage 2 GFR 60–89 mL/min/1.73 m^2; stage 3 GFR 30–59 mL/min/1.73 m^2; stage 4 GFR 15–29 mL/min/1.73 m^2; and stage 5 GFR <15 mL/min/1.73 m^2 [1]. Patients with stage 5 chronic kidney disease have ESRD which is often associated with lesions of organs and systems, such as cardiovascular disease, infection, anemia, gastrointestinal symptoms, bone disease, metabolic disorders, electrolyte, and acid-base imbalance. Some complications can be serious and life threatening. At this advanced stage of kidney disease, renal replacement therapy is needed to maintain excretion function, and treatment of the pathological changes of various systems and organs to sustain life. The resulting medical care costs bring heavy financial burdens to the family and society.

At present, the prevalence of chronic kidney disease showed a clear upward trend all over the world. According to the kidney disease data system (the National Health and Nutrition Examination Survey, NHANES) [2], the incidence of stage 1–4 chronic kidney disease was 10.0% in the United States between 1988 and 1994 and increased to 13.1% between 1999 and 2004. The rising incidence of diabetes, hypertension, and obesity is the main reason for the increase in the prevalence of chronic kidney disease. The prevalence of chronic kidney disease was 16.2% in Australia [3], 13.7% in South Korea [4], and 12.9% in Japan [5]. In China, the prevalence of chronic kidney disease in adults was 10.8% [6]. The prevalence has reached 13.0% in adults over 18 years old in Beijing [7] and 15.1% in adults over 30 in Handan rural areas of Hebei province [8]. The price of using blood glucose control to prevent the occurrence of complications of diabetes, to a certain extent, is making the blood sugar low, and therefore hypoglycemia should also be watched. Therefore, how to detect early chronic kidney disease and the high-risk population, control risk factors, delay the progression of the disease, and reduce the incidence of end-stage renal disease have become some of the most important public health problems in the world.

The glomerular capillary loops are the primary site of chronic kidney disease, and the retinal microvessel is considered as the principal site of retinopathy. Both of them belong to the microcirculation system. This raises the following question: Can the lesions of the retinal microvasculature reflect the abnormalities of the renal microcirculation? Previous studies have shown that the retinal microcirculation has the same anatomical and physiological characteristics as the microcirculation of brain, coronary vessels, and other organs [9]. The animal experiments also have confirmed that there is consistency in the pathogenesis of retinal and systemic microcirculation abnormalities [10]. In 1990, the Atherosclerosis Risk in Community (ARIC) Study evaluated the relationship between retinal vascular abnormalities and systemic diseases by using fundus photography and established the qualitative and quantitative evaluation criteria for retinal vasculopathy. Since then, the researchers have begun to use fundus photography techniques for the screening of systemic vascular disease. To date, a number of population-based epidemiological surveys have shown that retinal vasculopathy was associated with coronary heart disease [9, 11], stroke [12], hypertension [13–16], diabetes [11, 16, 17], and chronic kidney disease [17–22], suggesting that retinal vascular abnormalities can be used as an important clinical indicator to assess the risk of systemic disease.

26.2 Chronic Glomerular Disease and Retinal Vascular Abnormalities

According to the National Kidney Foundation's kidney disease outcome quality initiative (K/DOQI) in 2002, chronic kidney disease is defined as follows: (1) the presence of kidney damage (evidence may derive from the results of blood or urine test) for at least 3 months, with or without glomerular filtration rate (GFR) decrease, and (2) the presence of GFR <60 mL/min/1.73 m^2, for at least 3 months, with or without kidney damage [1].

Among the evidences of kidney damage, microalbuminuria is an early manifestation and associated with anatomic structure changes of the glomerulus, impairment of the charge barrier of the glomerular filtration membrane, reabsorption dysfunction of the renal tubule, and glomerular hemodynamic changes. Albuminuria is a marker of glomerular filter damage and reflects the severity of renal injury. The gold standard for diagnosing albuminuria is the 24-h or overnight urinary albumin excretion rate [23]. But its implementation is limited due to its susceptibility to influencing factors such as urine retention, test, and transportation and blood pressure fluctuation. Therefore, many guidelines recommend using next-day albumin creatinine ratio (ACR), which has good stability, as the criteria for diagnosing albuminuria [24, 25]. At present, there are mainly two kinds of diagnosis criteria as recommended by guidelines: (1) ACR ≥30 mg/g (3.39 g/mol) as recommended by the American Diabetes Association (ADA) [26] and (2) ACR ≥17 mg/g (1.92 g/mol)

for males and ACR ≥25 mg/g (2.83 g/mol) for females, as recommended by K/DOQI [27]. Although studies have shown that there is no significant difference in the average urinary albumin excretion rate between the sexes, experts believe that the incidence of albuminuria would be significantly lower in males than in females when using single criteria of ACR because urinary creatinine excretion rate is always higher in males than in females considering that males have higher muscle mass and creatinine is the metabolite of skeletal muscle [28]. Therefore, the latter type of criteria is more widely used [29–31].

In recent years, there have been several studies on the relationship between retinal vascular disease and chronic kidney disease, such as the US Cardiovascular Health Study (CHS) [29], the Atherosclerosis Risk in Communities Study (ARIC) [32], the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [22], the Singapore-Malay Eye Study (SiMES) [33], the Chinese Handan Eye Study (HES) [34], and the Beaver Dam Eye Study (BDES) [35]. It is generally believed that retinal vascular disease and chronic kidney disease have a certain correlation.

The US Cardiovascular Health Study (CHS) is a prospective, multicenter, cohort study [29]. The study defined retinal vascular abnormalities as retinopathy (hard and soft exudates, hemorrhages, or microaneurysms) and/or retinal arteriolar abnormalities (arteriovenous nicking, focal arteriolar narrowing, or arteriole-to-venule ratio reduction). After 4 years of observation, the researchers found that retinal vascular abnormalities were significantly associated with renal function deterioration. After adjustments for age, gender, race, weight, diabetes, hypertension, angiotensin-converting enzyme inhibitor use, and proteinuria, patients with retinopathy showed a significant increase in serum creatinine level [0.3 mg/dL increase in SCr (OR: 3.2, CI: 1.58–6.5)], and a significant decline in eGFR [20% or greater decline in eGFR (abbreviated MDRD equation) (OR: 2.84, CI: 1.56–5.16)] compared with those without retinopathy. These results were independent of the effects of any associated diabetes or hypertension. These observed findings suggest that patients with retinopathy are more likely to develop renal dysfunction. The reason may be that retinal vascular disease is the reflection of systemic microvascular damage, and there is a correlation between renal dysfunction and retinal vascular abnormalities.

The ARIC Study showed that retinal vascular abnormalities were associated with declining renal function and decreased cognitive ability [32]. After controlling for age, gender, race, diabetes, hypertension, and other risk factors, individuals with retinopathy (OR 2.0; 95% CI 1.4–2.8), microaneurysms (OR 2.0; 95% CI 1.3–3.1), retinal hemorrhages (OR 2.6; 95% CI 1.6–4.0), soft exudates (OR 2.7; 95% CI 1.6–4.8), and arteriovenous nicking (OR 1.4; 95% CI 1.0–1.9) were more likely to develop renal dysfunction than individuals without these abnormalities. It was also found that there was a correlation between retinopathy and elevated serum creatinine levels in individuals with diabetes/hypertension, or both or neither, although this association was sometimes not statistically significant. These findings suggested that individuals with retinopathy were more likely to develop renal dysfunction. The mechanism of kidney damage may not be directly due to the increased blood pressure or blood glucose; instead, common systemic microvascular processes may underlie the development of microvascular damage in the eye and kidney.

In the Singapore Malay Eye Study (SiMES) [33], it was found that, after controlling for age, gender, education, smoking, diabetes, hypertension, body mass index, and serum lipid level, the risk of occurrence of eGFR <60 mL/min/1.73 m^2 and albuminuria in individuals with the smallest CRAE (central retinal arteriolar equivalent) quartile was higher than those with the largest CRAE quartile [1.42 (95% CI 1.03–1.96) and 1.80 (95% CI 1.11–2.91) times, respectively]. Retinopathy was also found to be positively associated with both eGFR and albuminuria. However, retinal venular diameter was not associated with chronic kidney disease. These findings suggest that retinal arteriolar narrowing is associated with chronic kidney disease, independent of diabetes and hypertension. The retinal arteriolar narrowing is considered as a marker of microvascular damage caused by elevated blood pressure.

The Handan Eye Study (HES) showed that both retinal vascular abnormalities and retinal arteriole-to-venule ratio (AVR) were associated with albuminuria [34]. After controlling for age and gender, the smallest CRAE group had the highest rate of GFR decline and proteinuria, and the largest central retinal venular equivalent (CRVE) group also had the highest rate of GFR decline. Individuals with reduced CRAE, increased CRVE, and reduced AVR were more likely to have proteinuria (OR 1.27, 95% CI 1.04–1.54, $p = 0.02$) and the highest rate of GFR decline. Hypertension and diabetes are involved in the development of retinal vascular abnormalities and proteinuria. However, independent of diabetes and hypertension, individuals with retinal vascular abnormalities are more likely to develop proteinuria (OR 1.54, 95% CI 1.29–1.85, $p < 0.05$).

A total of 4594 adults aged 45–84 years were included in the Multi-Ethnic Study of Atherosclerosis (MESA) [36]. After a median follow-up of 4.8 years, there were 232 incidences of chronic kidney disease stage 3 cases. Overall, retinal microvascular caliber was not associated with the incidence of chronic kidney disease stage 3. However, in race-stratified analysis, whites with the lowest arteriolar caliber tertile had a 1.78 times higher risk of developing chronic kidney disease stage 3 compared with those with the highest arteriolar caliber tertile after controlling for multiple factors. This association even existed in whites who have neither diabetes nor hypertension. It was concluded that retinal vascular abnormalities may be associated with the progression of chronic kidney disease in whites.

The possible mechanism is that retinal arteriolar narrowing reflects microvascular damage caused by hemodynamic changes, such as intimal thickening, tunica media hyperplasia, hyaline degeneration, and sclerosis. Pathologic changes of the kidneys are associated with endothelial damage of the small vessels of the kidneys, mesangial cell proliferation, and decreased glomerular filtration area. Both retinal and renal arterioles have the same pathologic changes in microvascular damage. Therefore, retinal arteriolar narrowing has been suggested to be able to predict the risk of renal dysfunction.

However, there were discrepancies in the results of the studies on the relationship between changes in the calibers of retinal vessels and chronic kidney disease. The WESDR study showed that after adjusting for age, gender, duration of diabetes, HbA1c levels, retinopathy severity, and other factors, larger retinal venular diameter was associated with an increased risk of proteinuria (RR 1.53, 95% CI 1.19–1.97) and renal insufficiency (RR 1.51, 95% CI 1.05–2.17) [19]. However, changes in the diameter of retinal arteriole were not significantly associated with either proteinuria or renal insufficiency [19]. The ARIC study showed that in a population-based survey of a large sample size (over 10,000 people) lasting 6 years, retinal AVR was not associated with the development of renal dysfunction (an increase in serum creatinine of at least 0.4 mg/dL or a death or hospitalization as a result of chronic kidney disease) [32]. Similarly, in the

Table 26.1 Studies investigating the relationship between retinal vascular abnormalities and chronic kidney disease

Study	ARIC	CHS	WESDR	HES	SiMES
Population	Four US communities	Four US communities	Wisconsin (US)	Handan rural areas of Hebei province (China)	Asian (Singapore)
Year	1987–1989	1989–1990	1980–1996	2006–2007	2008
Age (years)	45–64	≥65	≥30	≥30	40–80
Eligible individuals (no.)	15,792	5201	10,135 diabetic patients	7577	4168
Participants (no.)	10,056	1394	557 type 1 diabetic patients	5925	3280
Criteria for renal function decline	Increase in serum creatinine of at least 0.4 mg/dL (difference between the second and fourth examinations) or a death or hospitalization as a result of chronic kidney disease	A 0.3 mg/dL or greater increase in serum creatinine levels (the difference between the blood Cr at 9 years and that at 5 years) or 20% or greater decrease in eGFR (abbreviated MDRD equation)	eGFR <60 mL/min/1.73 m^2; ACR ≥30 mg/g	eGFR <60 mL/min/1.73 m^2 or ACR ≥17 mg/g for males and ACR ≥25 mg/g for females	eGFR <60 mL/min/1.73 m^2 or ACR ≥17 mg/g for males and ACR ≥25 mg/g for females
Prevalence	Retinopathy (6.7%) Development of renal dysfunction (2.7%)	Retinopathy (10%) Retinal arteriolar abnormalities (50%) Renal function decline (5%)	eGFR decline (20.5%) Proteinuria (32.9%)	Retinal vascular abnormalities (15.4%) eGFR decline (0.4%) Proteinuria (16.5%)	eGFR decline (17.2%) Micro/macroalbuminuria (33.6%)
Relationship between retinal vascular abnormalities and chronic kidney disease	Individuals with retinopathy (OR 2.0; 95% CI 1.4–2.8) and arteriovenous nicking (OR 1.4; 95% CI 1.0–1.9) were more likely to develop renal dysfunction than those without	Participants with retinopathy were more likely to have a 0.3 mg/dL increase in serum creatinine level (OR 3.2, 95% CI 1.58–6.5) or 20% or greater decline in eGFR (OR 2.84; 95% CI 1.56–5.16)	Larger retinal venular diameter was associated with an increased risk of gross proteinuria (RR 1.53, 95% CI 1.19–1.97) and renal insufficiency (RR 1.51, 95% CI 1.05–2.17)	Individuals with retinal vascular abnormalities were more likely to develop proteinuria (people with diabetes: OR 1.93, 95% CI 1.19–3.13; people with hypertension: OR 1.45, 95% CI 1.05–2.02; people with diabetes and hypertension: OR 1.84, 95% CI 1.05–3.22)	Retinopathy was found to be positively associated with both micro/macroalbuminuria (OR 1.88, 95% CI 1.13–3.15) and eGFR of less than 60 mL/min/1.73 m^2 (OR 1.56, 95% CI 1.14–2.14); individuals with reduced CRAE were more likely to have chronic kidney disease than those with increased CRAE (micro/macroalbuminuria: OR 1.24, 95% CI 1.06–1.44; eGFR of less than 60 mL/min/1.73 m^2: OR 1.12, 95% CI 1.01–1.24)

Abbreviations: *ACR* urinary albumin-creatinine ratio, *ARIC* the Atherosclerosis Risk in Communities Study, *CHS* the Cardiovascular Health Study, *HES* the Chinese Handan Eye Study, *SiMES* the Singapore-Malay Eye Study, *WESDR* the Wisconsin Epidemiologic Study of Diabetic Retinopathy

CHS study, the presence of retinal arteriolar abnormalities (arteriovenous nicking, focal arteriolar narrowing, or the lowest quartile AVR) was not associated with deteriorating renal function (a ≥0.3 mg/dL increase in serum creatinine level or ≥20% decline in eGFR) in 1394 elders [29]. In addition, the AusDiab study also found that the AVR was not associated with microalbuminuria and GFR in individuals with impaired glucose metabolism [37]. In the Beaver Dam Eye Study, although there was a trend of eGFR decrease in the narrowest retinal arteriolar diameter quartile and widest venular diameter quartile, baseline retinal arteriolar and venular diameters were not associated with 15-year risk of incidence of CKD [35]. Therefore, it was suggested that retinal arteriolar narrowing and eGFR decrease may share mechanisms, but are not causally related. The reasons for these discrepancies are probably due to differences in the race, gene, primary disease, ages, and research methods of the study groups, and the relationship between the eye and the chronic kidney disease still needs further investigation.

Studies investigating the relationship between retinal vascular abnormalities and chronic kidney disease are summarized in Table 26.1.

26.3 Hypertension, Renal Damage, and Retinal Vascular Abnormalities

Hypertension is a systemic disease characterized by persistently elevated arterial blood pressure, and elevated arterial pressure is the main pathophysiological change and clinical manifestation of hypertension. Systemic arteriospasm and arteriosclerosis are the basic conditions for persistent elevation of arterial pressure. Meanwhile, long-term increase of blood pressure can cause damages to the heart, brain, kidney, peripheral blood vessels, fundus, and other target organs. The central retinal artery is the only small artery that can be noninvasively observed in vivo. The condition of the fundus in the course of hypertension may reflect the degree of damages in target organs, which is of great significance to the diagnosis and prognosis of hypertension.

In the early nineteenth century, Robert Marcus Gunn, a famous ophthalmologist, found that high blood pressure could cause damage to the retinal vascular system. Since then, many studies have shown that progressive visual deterioration occurs when hypertension affects the fundus of the eye, and ocular fundus changes are related to the degree of hypertension and its prognosis.

Hypertensive retinal vascular changes mainly include the following aspects [37, 38]: (1) Retinal arteriospasm: It is the first fundus sign of primary hypertension, and is the basis of all hypertensive retinopathies. The severity of the retinal arteriospasm was positively correlated with the degree of increased arterial pressure. Under the continuous effects of hypertension, the retinal AVR can be changed from normal 2:3–1:2–3, or even 1:4. (2) Retinal arteriosclerosis: The vessel walls develop hyaline degeneration because of vasospasm, ischemia, and hypoxia. Hypertrophy and hyperplasia of smooth muscle cells contribute to vascular wall remodeling and luminal narrowing. Clinical manifestations include retinal arteriolar narrowing, arteriovenous crossings (AV nicking), changes of arteriolar light reflex (silver or copper wiring), arteriolar tortuosity, and an increase in arteriolar bifurcation angle. (3) Retinal venous changes: Hypertensive retinopathy mainly involves the retinal arterioles, while diabetic retinopathy mainly involves the retinal venules. The retinal veins are found to be engorged when the retinal arteries are in spasm. (4) Retinopathy other than retinal vascular changes: In addition to vascular changes, primary hypertension can also lead to diffuse retinal edema, hemorrhages, hard exudation, cotton wool spots, choroidal lesions, and optic disc edema. Table 26.2 shows the staging of hypertensive retinopathy.

Animal experiments have confirmed that the pathological changes of the retinal arterioles and renal arterioles in the hypertensive rat model are highly correlated [39]. The caliber of the afferent arteriole in the glomeruli of hypertensive rats was narrower than that in the control group even before the onset of hypertension [40]. Hypertension can lead to increased glomerular capillary pressure, glomerular hyperperfusion, and hyperfiltration. The vasoconstriction and vasodilation of the renal arterioles (e.g., glomerular afferent and efferent arterioles) were regulated through self-adjustment mechanism so as to maintain stability of the renal blood flow and glomerular filtration rate under the condition of arterial hypertension, which ensures to eliminate the metabolic wastes normally and balance the body fluid. Persistently elevated blood pressure can cause renal arteriosclerosis, resulting in glomerular damage, whereas renal dysfunction can affect the stability of the renal hemodynamic regulation system, leading to high blood pressure. So hypertension and kidney damage have a reciprocal causation relationship [41]. Microalbuminuria is an early marker of glomerular injury and also an early evidence for clinical assessment of hypertensive nephropathy. It has long been proved that hypertension is an important independent predictor of the development and progression of chronic kidney

Table 26.2 Classification of hypertensive fundus changes

Group 1	Mild narrowing, sclerosis, spasm, and tortuosity of the retinal arterioles
Group 2	Moderate narrowing and sclerosis of the retinal arterioles, exaggeration of the light reflex, and arteriovenous nicking
Group 3	Severe narrowing of retinal arterioles with focal constriction, and retinal edema, cotton wool spots, and hemorrhage are also present
Group 4	Changes in Group 3 plus papilledema

disease and the increased mortality in patients with chronic kidney disease.

Population studies have shown that arteriolar narrowing in high blood pressure is not only a sign of hypertensive damage, but may also be the original event of the occurrence and progression of hypertension [42]. Retinal arteriolar narrowing may occur before the elevation of arterial blood pressure and increase the risk of hypertension. The ARIC study found that 14.4% of participants developed high blood pressure after a 3-year follow-up in healthy subjects who had never had a history of hypertension [43–45]. The AVR was inversely proportional to the incidence of hypertension (for AVRs from the highest to the lowest quintile, the incidences of hypertension were 8.9%, 12.3%, 13.7%, 14.3%, and 22.3%, respectively). After controlling for the confounding factors, the OR value of hypertension was 1.62 (95% CI, 1.21–2.18) in participants with low A/V ratio, and 1.61 (95% CI, 1.27–2.04) in participants with localized retinal arteriolar narrowing. Individuals with focal retinal arteriolar narrowing had a 60% increase in the risk of developing hypertension at 3 years compared with those without (the incidence of hypertension in the two groups was 25.1% and 13.0%, respectively). For any degree of generalized narrowing, individuals with focal narrowing had a mean arteriolar blood pressure (MABP) approximately 8 mmHg higher than those without ($p < 0.0001$). The incidence of focal retinal arteriolar narrowing, arteriovenous nicking, and retinopathy was positively correlated with blood pressure level. For every 10 mmHg increase in MABP, AVR decreased by 0.02 unit ($p < 0.0001$), focal arteriolar narrowing had an OR of 2.00 (95% CI, 1.87–2.14), arteriovenous nicking had an OR of 1.25 (95% CI, 1.16–1.34), and retinopathy had an OR of 1.25 (95% CI, 1.15–1.37). Furthermore, both generalized retinal arteriolar narrowing and arteriovenous nicking were significantly associated with elevated blood pressure in 3–6 years.

The Beaver Dam Eye Study (BDES) showed that the CRAE was negatively correlated with blood pressure [34]. For every 10 mmHg increase in systolic blood pressure (SBP), CRAE decreased by 4.4 μm (95% CI, 3.8–5.0). It was also found that the correlation was more obvious in the younger population: for every 10 mmHg increase in SBP, CRAE decreased by 7.0 μm in the 43–54 age group, whereas by 2.5 μm in the 75–84 age group. These findings suggested that the magnitude of the reduction in CRAE did not increase with age, which may be due to the fact that heavier retinal arteriosclerosis in the older population partly offsets the arteriolar narrowing caused by hypertension. The BDES also showed that the odds ratio comparing the smallest with the largest A/V ratio quartile was found to be 1.82 (95% CI, 1.39–2.40) for hypertension [34], suggesting that alterations in the microvasculature system may contribute to the development of hypertension. The main pathophysiologic characteristic of hypertension is microvasculopathy, especially the constriction of peripheral arterioles. The continuous constriction of these arterioles increases peripheral vascular resistance, leading to the development and progression of hypertension. Meanwhile, persistently elevated arterial pressure can aggravate the vasculopathy, forming a vicious circle [46].

The Blue Mountains Eye Study (BMES) also found that the diameters of the retinal vessels decreased as arterial blood pressure increased [47–49]. CRAE, CRVE, and AVR were all correlated with blood pressure. For every 10 mmHg increase in MABP, CRAE, CRVE, and AVR decreased by 3.5 μm, 0.96 μm, and 0.012, respectively. Moreover, after 5 years of follow-up, generalized retinal arteriolar narrowing at baseline was associated with increased risk of incident severe hypertension (odds ratio 2.6; 95% CI, 1.7–3.9) when comparing the narrowest versus widest quintile. These findings support the hypothesis that retinal vascular abnormalities could predict the severity and duration of hypertension. At the same time, it was confirmed that hypertensive individuals without treatment or with suboptimal control were more likely to have retinal vascular abnormalities than those with better blood pressure control.

In the Cardiovascular Health Study (CHS) [50], after analyzing the fundus photographs in participants aged 69–97 years without diabetes, it was found that all retinal lesions were associated with hypertension (the OR values of retinopathy, focal arteriolar narrowing, arteriovenous nicking, and generalized arteriolar narrowing were 1.8, 2.1, 1.5, and 1.7, respectively). Retinal vascular abnormalities are related to not only elevated concurrent blood pressure, but also previously elevated blood pressure. After adjustment for concurrent blood pressure, generalized arteriolar narrowing and arteriovenous nicking were significantly correlated with blood pressure levels over the past 8 years [51]. These data suggested that generalized retinal arteriolar narrowing and arteriovenous nicking were signs of microvascular injuries caused by chronic hypertension, whereas focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton wool spots were associated with recent blood pressure levels, which may reflect the severity of recent hypertension.

The Rotterdam Study also investigated the relationship between retinal arteriolar narrowing and hypertension, and found that individuals with retinal arteriolar narrowing (OR 1.38; 95% CI 1.23–1.55) and venular narrowing (OR 1.17; 95% CI 1.04–1.32) were more likely to develop hypertension than those without these abnormalities, suggesting that both retinal arteriolar and venular narrowing may precede the development of systemic hypertension [52]. It was speculated that microvascular impairment (such as renal arteriolar damage and retinal arteriolar narrowing) caused by a variety of factors may lead to blood pressure elevation and progression, further aggravating the damage to the corresponding target organs.

Many studies have confirmed that retinal arteriolar narrowing is a sign of microvascular involvement in persistent hypertension and metabolic disturbances. Retinal arteriolar narrowing is associated with hypertension independently. Both generalized and focal arteriolar narrowing can predict the risk of target organ damage in hypertensive individuals with normal blood pressure. Quantitative examination of the retinal vascular caliber can be used to monitor the effects of blood pressure, whereas optimal control of blood pressure contributes to alleviated vascular lesions [36, 53, 54].

Based on the latest retinal vessel image analysis technique, the Hoorn Study confirmed that there was a correlation between generalized retinal arteriolar narrowing and cardiovascular risk factors such as elevated blood pressure and decreased renal function, and CRAE in the smallest group was associated with renal dysfunction in normotensive and hypertensive individuals. There are two important findings in this study: (1) the incidence of chronic renal insufficiency was negatively correlated with CRAE (the incidence of renal insufficiency in the smallest and largest CRAE group was 7.8% and 3.8%, respectively) and (2) it was nearly six times more likely to develop kidney disease in individuals with hypertension and small CRAE than those without, suggesting that the coexistence of hypertension and small CRAE is highly associated with kidney damage, independent of race, gender, age, and conventional risk factors [54].

The Handan Eye Study (HES) investigated the retinal vascular abnormalities, kidney disease, and its risk factors in adults over 30 years old in Handan rural areas of Hebei province. The results found that the prevalence of CKD was 15.1% in participants over 30 years old in rural areas of Handan, and age, hypertension, diabetes mellitus, female, etc. were risk factors for CKD. Changes in retinal vascular diameter were associated with the occurrence of hypertension, diabetes, and albuminuria. This is manifested as follows: (1) The study showed that after adjustments for age, gender, BMI, high-density lipoprotein, low-density lipoprotein, total cholesterol, triglyceride, diabetes, hypertension, smoking, education, and other factors, retinal arteriolar narrowing was independently associated with the occurrence of albuminuria. The odds ratio comparing the smallest with the largest CRAE group was found to be 1.24 (95% CI, 1.02–1.51) for albuminuria. The increase in blood pressure was positively correlated with the occurrence of albuminuria, and the risk of albuminuria was 1.41 times higher (95% CI: 1.21–1.64) in the hypertensive group than in the normotensive group. The OR value of albuminuria was 2.06 (95% CI, 1.54–2.76) in participants with SBP ≥180 mmHg. For every 10 mmHg increase in SBP, the incidence of albuminuria increased by 1.11 times (95% CI, 1.08–1.15). The OR value of albuminuria was 3.10 (95% CI, 1.77–5.45) in participants with diastolic blood pressure (DBP) ≥110 mmHg. For every 10 mmHg increase in DBP, the incidence of albuminuria increased by 1.17 times (95% CI, 1.11–1.24). It is particularly important to note that in normotensive individuals, the risk of albuminuria in the smallest CRAE group was also increased by 1.36 times (95% CI, 1.00–1.84) compared with that in the largest CRAE group. There was an even higher risk of developing albuminuria in individuals with coexistence of hypertension and reduced CRAE. (2) In participants with diabetes mellitus, the incidence of albuminuria was significantly higher in those with retinal vascular abnormalities than those without, and the vascular abnormalities were mainly characterized by increased CRVE. In addition, the greater the CRVE, the higher the prevalence of diabetes. These findings suggest that hypertension may have a greater effect on the retinal arterioles, whereas diabetes may have a greater effect on the retinal venules. Retinal arteriolar narrowing and venous dilatation may to a certain extent reflect the development of hypertension and diabetes, and the decrease of retinal arteriovenous ratio is related to the occurrence of proteinuria. Therefore, it was hypothesized that retinal vasculopathy may increase the risk of hypertension, diabetes, and kidney damage, and fundus examination may be helpful for the early detection of CKD, hypertension, and diabetes mellitus [34, 55, 56].

Persistently elevated arterial pressure in hypertension can lead to retinal vasculopathy, renal arteriosclerosis, and other target organ damage. Meanwhile, abnormalities in the microcirculation system can also affect the systemic blood pressure. There is a correlation between retinal arteriolar narrowing, elevated blood pressure, and occurrence of albuminuria. The possible mechanisms are as follows: (1) Microcirculation damage: Microcirculation refers to the blood circulation between the arterioles and venules, where the material is exchanged between the blood and the tissue. Microcirculation can regulate blood flow through the tissue, thereby affecting the systemic arterial pressure and venous return flow. However, many factors such as hypertension, diabetes mellitus, electrolyte disturbance, acid-base imbalance, tissue ischemia, and hypoxia can affect the function of microcirculation, creating an imbalance in the body's internal environment. The glomerular and retinal vessels are part of the microcirculation system, both of which have the general characteristics of the microvasculature and the special characteristics of the organs. Both the glomerular afferent arterioles and retinal arterioles belong to arterioles pathologically and precapillary resistance vessels physiologically. Because of the distribution characteristics of glomerular vessels (i.e., two capillary networks connected in series by efferent arterioles), the glomerular capillary pressure is high and can reach 40–60% of the average blood pressure of the aorta, which is beneficial for the plasma filtration by glomeruli. The caliber of the efferent arterioles is relatively small and the resistance is relatively high, so the blood pressure drop is prominent when the blood flows through this segment, which

is beneficial to the tubular reabsorption. The retinal vessels are an important part of the cerebral vascular network and have a high demand for blood oxygen. They are composed of retinal arteries and veins. Retinal arterioles belong to precapillary resistance vessels and regulate the retinal blood supply through vasoconstriction and vasodilation, whereas retinal venules are postcapillary resistance vessels and regulate the retinal capillary pressure through vasoconstriction and vasodilation, thereby affecting the exchange of substances and liquids between the blood and the tissue. The glomerular and retinal blood vessels are part of the systemic microcirculation, so systemic microcirculation impairment and internal environment imbalances caused by a variety of factors would alter the hemodynamics of kidney and retina, compromising organs' function. The glomerular and retinal vessels have similarity in the organizational structure and physiological function, so when exposed to the same risk factors both retinal and renal microcirculation would be damaged. Meanwhile, the microcirculation damage of retina and kidney as well as the whole body could influence the systemic arterial pressure, and then promote the development and progression of hypertension. (2) Endothelial dysfunction: Endothelial dysfunction is the common pathological mechanism of hypertension, retinal vasculopathy, and renal arteriosclerosis. Vascular endothelial cells play an important role in regulating vasomotor activity, stabilizing blood flow, and reconstructing blood vessels. Many factors can affect the vascular endothelial functions, such as hypertension, diabetes, genetic factors, hyperlipidemia, and smoking. In the case of hypertension, vascular endothelial cells are constantly exposed to increased shear stress generated by persistently elevated peripheral resistance, causing endothelial cell dysfunction. The secretion of vasodilators such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarization factor is reduced, whereas the secretion of vasoconstrictors such as endothelin and thromboxane A2 is increased. These factors, coupled with local renin-angiotensin system (RAS) activation, neurohumoral regulation imbalance, inflammation, smoking, blood glucose, and serum lipid abnormalities, can lead to hypertrophy and hyperplasia of smooth muscle cells, hyaline degeneration of vascular walls, and luminal narrowing, causing damage to the target organs. Meanwhile, microvascular endothelial dysfunction can in turn affect the systemic arterial pressure through the impairment of corresponding organ function. (3) RAS activation: The RAS is commonly known to regulate blood pressure, water, and electrolyte homeostasis, and maintains the stability of the human body's internal environment. The RAS exists not only in the circulatory system, but also in the vascular wall, heart, central nervous system, kidney, adrenal gland, etc., and participates in the regulation of the target organs. Excessive activation of the RAS can lead to sustained mass release of angiotensin II (Ang II), which causes vasoconstriction, acceleration of heartbeat, enhanced catecholamine and aldosterone secretion, and blood volume expansion by combination with its corresponding receptors (angiotensin II receptor types 1 and 2) distributed in heart, kidney, and blood vessels. Long-term activation of RAAS is closely related to the persistence and progression of hypertension, cardiac hypertrophy induced by hypertension, remodeling of heart and vessels, and pathophysiological mechanisms of target organ damage. The kidneys are the major organ involved in the synthesis and regulation of RAS. Furthermore, the kidneys are rich in blood circulation, accounting for 20–25% of cardiac output. Therefore, they can maintain the renal blood flow and GFR through autoregulation and neurohumoral regulation when there are profound changes in systemic hemodynamics, to ensure the discharge of metabolic wastes and maintain fluid balance. The RAS is an important part of the renal neurohumoral regulation function, which is controlled by the renal blood flow, and it regulates the formation of Ang II by adjustment of renin release from the juxtaglomerular apparatus. In addition, recent studies have shown that ocular tissue also has the ability to synthesize RAS independently, and the RAS activation is also involved in the pathogenesis of retinopathy [56].

26.4 Diabetes, Diabetic Retinopathy, and Diabetic Nephropathy

Diabetes is a metabolic disorder of glucose metabolism caused by genetic and environmental factors. It's manifested as carbohydrate, lipid, protein, water, and electrolyte abnormalities due to absolute or relative deficiency of insulin. According to the pathogenesis, diabetes can be divided into four categories: type 1 diabetes, type 2 diabetes, special types of diabetes, and gestational diabetes. Chronic hyperglycemia is a major feature of diabetes, and hypertension, hyperlipidemia, and other metabolic disorders are major complications of diabetes.

Diabetic microangiopathy, commonly seen in the retina, kidneys, nerves, skin, muscle, and other tissues, is a major chronic complication of diabetes. The glucose uptake by the kidneys, lens, retina, etc. during hyperglycemia is independent of insulin, resulting in consistently increased levels of glucose in the tissue. Excessive glucose produces sorbitol via aldose reductase, which is rarely metabolized, thereby causing intracellular hypertonicity and leading to cell damage. Chronic hyperglycemia plays a critical role in the development and progression of diabetic microangiopathy. Hypertension, dyslipidemia, obesity, systemic vascular inflammation, and endothelial damage are the risk factors for diabetic microangiopathy [57, 58].

Diabetic retinopathy (DR) refers predominantly to structural abnormalities of the retinal microvessels as a result of

damage to the originally highly coordinated retinal cell components by hyperglycemic environment, mainly related to factors secondary to hyperglycemia such as retinal metabolic abnormalities, polyol hypermetabolism, protein saccharification, and increased oxidative stress. The pathological changes of DR mainly include the disappearance of retinal microvascular pericytes, the formation of capillary microaneurysms, and the thickening of the microvascular basement membrane, leading to blood-retinal barrier disruption, endothelial cell swelling, capillary occlusion, ischemia of retinal vascular intima, and neovascularization and eventually resulting in vision impairment. The fundus manifestation includes retinal microaneurysms, hemorrhages, hard exudates, cotton wool spots, macular edema, ischemic maculopathy, vitreous hemorrhages, proliferative retinopathy, and optic neuropathy, ultimately contributing to retinal detachment and vision loss. Therefore, diabetic retinopathy is one of the important causes of acquired blindness. At present, diabetic retinopathy is classified into five categories [59] (Table 26.3).

Diabetic nephropathy is one of the most serious complications of diabetes, and it is also an important cause of mortality in diabetes. Hyperglycemia can act directly on glomerular mesangial cells and vascular smooth muscle cells, causing vasodilation of glomerular afferent arterioles via oxygen free radical production and resulting in glomerular hypertension. Hyperglycemic condition in diabetes facilitates the irreversible formation of advanced glycation end products (AGEs) that are formed as a result of a series of reactions between reducing sugars and proteins. Accumulation of AGEs can lead to a series of functional and morphological changes in the glomerulus. High glucose can increase triglyceride production, activate protease C, and enhance extracellular matrix synthesis. High glucose can also activate the hexosamine biosynthetic pathway and glycosylate protein, and it can affect the expression of TGF-β and plasminogen activator inhibitor 1 (PAI-1). In addition, elevated glucose concentration is also known to alter renal hemodynamics, causing intraglomerular "three highs" (high pressure, high perfusion, and high filtration). Increased urinary glucose excretion leads to increased absorption of glucose by tubules, which is accompanied by enhanced reabsorption of sodium, resulting in water and sodium retention and hypertension. The pathological hallmark of diabetic nephropathy in renal glomerulus is the expansion of the mesangial matrix and thickening of the capillary basement membrane. The charge-selective barrier of the glomerular filter is damaged in early stages of diabetic nephropathy resulting in microalbuminuria and selective proteinuria. With the progression of the disease, the size-selective barrier of the glomerular filter is impaired, and nonselective proteinuria gradually occurs. Once the destructive process becomes advanced, the end-stage kidney has a monotonous appearance of glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Therefore, clinical course of diabetic nephropathy is divided into five stages. The GFR is increased by 20–40% more than normal at the earliest stage, followed by the gradual emergence of microalbuminuria, and then the massive proteinuria. Once massive proteinuria occurs, the majority of patients will progress to end-stage kidney disease and uremia.

Table 26.3 Classification of diabetic retinopathy

Severity	Lesions present
No diabetic retinopathy	No retinal lesions
Mild nonproliferative diabetic retinopathy	Microaneurysm only
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe nonproliferative diabetic retinopathy
Severe nonproliferative diabetic retinopathy	One or more of the following changes: 1. Severe hemorrhages in all four quadrants 2. Significant venous beading in two or more quadrants 3. Significant intraretinal microvascular abnormalities (IRMA) in one or more quadrants No signs of proliferative diabetic retinopathy
Proliferative diabetic retinopathy	Neovascularization, vitreous or preretinal hemorrhages

At present, diabetic nephropathy has become a major cause of end-stage renal disease in China. In 2012, a regional population survey of the largest sample size in the world was published in Lancet, and the results showed that the risk of developing CKD was significantly increased in diabetic than in nondiabetic individuals. The study was the largest epidemiological investigation of CKD in China, which lasted 4 years, involving 13 provinces and cities in China, and nearly 50,000 adults over 18 years old were investigated for CKD and its associated risk factors. The results showed that individuals with diabetes had a 100% increase in the risk of eGFR of <60 mL/min/1.73 m^2 and a 99% increase in the risk of albuminuria compared with those without [6]. The 2012 annual report of Beijing Blood Purification Quality Control and Improvement Center also showed that diabetic nephropathy is the leading cause of renal failure in patients referred for uremia therapy [60].

According to urine tests, renal function, and pathological changes, clinical course of type I diabetic nephropathy is divided into five stages (Table 26.4), which can also be used for reference in type II diabetic nephropathy classification.

Diabetic retinopathy and diabetic nephropathy often clinically coexist with each other.

The WESDR showed that the prevalence of diabetic retinopathy was related to the duration of diabetes, and changes in CRVE were associated with proteinuria and renal damage.

Table 26.4 Stages of diabetic nephropathy

Stage	GFR	UAER	BP	Main features
1	Increased 20% to 40%	Normal	Normal	Kidneys enlarge in size and GFR is higher than normal
2	Increased	Normal	Normal	Microalbuminuria can be noticed after intense physical activity
3	Normal	Persistent positive	Increased but not exceeding normal	
4	GFR starts to decline	Clinical proteinuria	Develop high blood pressure	Nephrotic syndrome may develop and renal function declines
5	End-stage renal failure			Clinical features of uremia occur

The prevalence of diabetic retinopathy varied from 17% in persons who had type 1 diabetes for less than 5 years to nearly 100% in persons who had diabetes for 15 or more years [61]. The prevalence of diabetic retinopathy varied from 29% to 78% in persons with type 2 diabetes for less than 5 years and 15 or more years, respectively [62]. Insulin-using persons with cholesterolemia are more likely to develop hard exudate [63]. These findings suggested that the longer the duration of diabetes, and the higher glycosylated hemoglobin and blood pressure levels, the more likely it was to develop diabetic retinopathy. In addition, the WESDR found that type 1 diabetes with more severe retinopathy is associated with an increased risk of diabetic nephropathy within 10 years. The relative risk of developing renal insufficiency within 10 years was 9.54 (95% CI, 1.94–47.04) in individuals with moderate nonproliferative retinopathy at baseline and 24.73 (95% CI, 7.58–80.67) in those with proliferative retinopathy at baseline [64]. After 16 years of observation, the WESDR confirmed that in individuals with type 1 diabetes, larger retinal venular diameter was independently associated with the long-term incidence of gross proteinuria and renal insufficiency (GFR <60 mL/min/1.73 m^2) [19]. After adjusting for age, gender, duration of diabetes, HbA1c levels, and other factors, larger retinal venular diameter was associated with an increased risk of gross proteinuria (RR 1.53, 95% CI 1.19–1.97) and renal insufficiency (RR 1.51, 95% CI 1.05–2.17) [19]. The Handan Eye Study also found that the greater the CRVE, the higher the prevalence of diabetes, and both of them have a certain correlation with proteinuria [33]. The Rotterdam study found that increase in retinal vein caliber is associated with impaired fasting glucose regulation and development of type 2 diabetes. Retinal venule dilation is related to inflammation and endothelial damage, and may be associated with retinal local hypoxia and venous blood stasis [65–67]. In addition, studies also showed that experimentally induced hyperglycemia in nondiabetic individuals can lead to retinal vein dilatation, suggesting that hyperglycemia may have a direct dilatation effect on the retinal veins [68].

The CHS found that diabetic retinopathy was independently associated with progressive renal impairment, and pathological changes in renal microvasculature were significantly associated with changes in the microvasculature of the retina. Participants with diabetic retinopathy were more likely to have an observed significant deterioration in renal function, defined as a 0.3 mg/dL increase in serum creatinine level (OR 3.2, 95% CI 1.58–6.5) or 20% or greater decline in eGFR (OR 2.84; 95% CI 1.56–5.16) [18]. In separate stratified analyses of patients with type 2 diabetes, the diabetic retinopathy had significant correlation with microalbuminuria and massive proteinuria. The risk of retinopathy was significantly increased in patients with microalbuminuria (OR 3.22, 95% CI 1.74–5.97) and massive proteinuria (OR 3.14, 95% CI 1.33–7.44) [69]. The ARIC Study reported that diabetic retinopathy such as microaneurysms, retinal hemorrhages, and soft exudates was associated with increased risk of renal dysfunction, and the OR values were 2.0 (95% CI 1.3–3.1), 2.6 (95% CI 1.6–4.0), and 2.7 (95% CI 1.6–4.8), respectively [20]. The study by Fan and associates reported that the incidence of diabetic nephropathy was positively correlated with the severity of diabetic retinopathy. The incidences of diabetic nephropathy in diabetic patients without diabetic retinopathy, diabetic patients with nonproliferative diabetic retinopathy, and diabetic patients with proliferative diabetic retinopathy were 5%, 42%, and 71%, respectively [70]. In a 4-year follow-up study of 413 participants with type 2 diabetes conducted in Hong Kong [71], macroalbuminuria was significantly associated with the progression of diabetic retinopathy (OR 6.77, 95% CI 2.16–21.23, $p = 0.001$). The incidence of albuminuria or proteinuria was significantly higher in subjects with progression of diabetic retinopathy than those without (42.9% vs. 15.2%, $p = 0.001$) [71]. In addition, the study by Boelter and associates also confirmed that proliferative diabetic retinopathy was associated with microalbuminuria in patients with type 2 diabetes, and diabetic nephropathy was positively associated with proliferative diabetic retinopathy [72]. Therefore, it is recommended that all type 2 diabetic patients with proliferative diabetic retinopathy should undergo renal function tests, including urinary protein measurements.

Diabetic retinopathy and diabetic nephropathy are the two main microvascular complications of diabetes, and they often clinically coexist with each other. The pathological changes of them are highly similar, suggesting that they may share a common pathophysiological basis, such as abnormal polyol and myoinositol metabolism, protein glycosylation, oxidative stress, DG-PKC system activation, inflammatory mediator release, apoptosis, and endothelial injury caused by hyperglycemia. Recent studies have shown that the RAS is involved in

the development and progression of diabetic retinopathy and diabetic nephropathy [57]. The retina has an independent RAS system, and the retinal local Ang II and angiotensin-converting enzyme (ACE) activities were both increased in diabetic retinopathy. The intraocular concentration of Ang II is related to the severity of diabetic retinopathy. The higher the Ang II concentration, the more severe the lesion is. Furthermore, the serum renin level in patients with diabetic retinopathy not only is a marker of the severity of retinopathy, but also reflects the renal function of the patients. The serum renin level is increased in active diabetic retinopathy, accompanied by the exacerbation of diabetic retinopathy and diabetic nephropathy. Ischemia and hypoxia are considered to be the common risk factors of ocular and renal damage [73, 74]. They lead to endothelial cell functional impairment, increased 5-hydroxytryptamine release, and retinal vein dilatation, accompanied with increased central retinal vein pressure and capillary permeability, thereby causing bleeding, exudation, etc. Ischemia and hypoxia can also lead to RAAS activation, excessive release of oxygen free radical in kidney, and disturbance of synthesis and secretion of nitric oxide and prostaglandin, thereby affecting the kidneys. Therefore, blocking RAAS may be of great value in preventing and treating diabetic retinopathy [42].

The pathogenesis of diabetic retinopathy may be related to race, gene, environment, and other factors. The Multi-Ethnic Study of Atherosclerosis (MESA) reported that the diabetic retinopathy prevalence rates among individuals with diabetes were 36.7% in blacks, 37.4% in Hispanics, 24.8% in whites, and 25.7% in Chinese. The main risk factors for diabetic retinopathy in blacks were diabetes duration, hypertension, and hyperlipidemia. However, these risk factors could not explain why Hispanics had similar diabetic retinopathy prevalence [75–77]. The Diabetes Control and Complications Trial (DCCT) observed 1441 diabetics and confirmed that the higher the body mass index and waist-to-hip ratio, the more likely it is to develop diabetic retinopathy. This study also confirmed that good glycemic control is very important for delaying the development and progression of diabetic retinopathy [78]. In addition, the UK Prospective Diabetes Study (UKPDS) for type 2 diabetes has further shown that controlling blood pressure can also delay the development of diabetic retinopathy and other microvascular endpoints [79]. These findings suggest that ethnic, genetic, and environmental factors also play a role in the development of diabetic retinopathy.

26.5 Retinal Vascular Abnormalities and Other Systemic Organ Damage

Many factors are involved in retinal vascular abnormalities and systemic organ damage.

The BDES showed that retinal vascular abnormalities can be found in 10–14% of individuals over 40 years without a definite history of diabetes [80], and results from the BMES confirmed that 1.2–1.8% of persons in this age group without diabetes develop retinal vascular abnormalities per year [81]. The pathogenesis of such nondiabetic lesions is unclear as yet, although hypertension, age, and impaired glucose tolerance are believed to play a role [82, 83].

The ARIC study found that the prevalence of hypertensive retinopathy was two times higher in African-Americans than in whites without diabetes, suggesting that the prevalence of retinopathy lesions in the nondiabetic population may vary by ethnicity [84]. In the whole cohort of the ARIC Study (i.e., persons with and without diabetes), the prevalence of stroke was 2–3 times higher in individuals with retinopathy than those without [85]. When retinopathy coexisted with cerebral white matter hypoxia on MRI, the risk of stroke and congestive heart failure increased by 20 times and 2 times, respectively [86]. These associations were independent of the effects of gender, age, hypertension, diabetes, smoking, dyslipidemia, and other cardiovascular risk factors.

In the BMES, retinopathy lesions in persons without diabetes also predicted almost twofold higher risk of stroke and stroke mortality [87]. The CHS showed that retinopathy is associated with atherosclerotic cardiovascular disease in diabetic populations [69]. Carotid stenosis is associated with retinopathy lesions in the absence of diabetes [50]. These findings provide a clue that the presence of systemic microcirculatory disease may lead to retinal vascular abnormalities in the nondiabetic population.

In the HES Study, most people with retinal vascular abnormalities are elderly and those with relatively high blood lipids, high body mass index, high CRP concentrations, high prevalence of hypertension and diabetes, high rates of smoking and drinking, and low incomes. These results suggested that aging can lead to degenerative changes in retinal vessels, and factors such as hypertension, diabetes, hyperlipidemia, and microinflammatory state can lead to abnormalities of the retinal microcirculation. Alcohol can dilate blood vessels; smoking can reduce the ability of blood to carry oxygen, thereby causing chronic hypoxia, endothelial cell injury, and increased 5-hydroxytryptamine release and resulting in retinal vessel dilation. In addition, low-income people in the study are mainly in the smallest CRAE group and the largest CRVE group. In these two groups, the prevalences of hypertension, diabetes, and proteinuria were also the highest, which may be due to poor health awareness and medication compliance of the low-income population [55]. These abovementioned factors may also contribute to the renal microcirculation abnormalities.

In summary, many factors can cause damage to the microcirculation of the body, and microcirculation abnormalities

can reflect the pathological changes of the organs and systems. Retinal vessels provide an open window to scrutinize the systemic microcirculation. The observed changes in retinal vessels, together with the examination of the corresponding organs, can be used to detect and evaluate systemic diseases. For the kidneys, the combination of fundus examination with renal function tests may be of practical clinical significance for early detection, early diagnosis, and early treatment of chronic kidney disease.

References

1. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39:S1–S266.
2. Snyder JJ, Foley RN, Collins AJ. Prevalence of CKD in the United States: a sensitivity analysis using the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis. 2009;53(2):218–28.
3. Si C, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. Am J Soc Nephrol. 2003;14(7 Suppl 2):S131–8.
4. Kim S, Lim CS, Han DC, et al. The prevalence of chronic kidney disease (CKD) and the associated factors to CKD in urban Korea: a population-based cross-sectional epidemiologic study. J Korean Med Sci. 2009;24(Suppl):S11–21.
5. Imai E, Horio M, Iseki K, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11:156–63.
6. Zhang LX, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet. 2012;379:783–822.
7. Zhang LX, Zhang PH, Wang L, et al. Prevalence and factors associated with CKD: a population study from Beijing. Am J Kidney Dis. 2008;51:373–84.
8. Jiang LP, Liang YB, Qiu B, et al. Metabolic syndrome and chronic kidney disease in a rural Chinese population. Clin Chim Acta. 2011;412:1983–8.
9. Wong TY, Klein R, Klein BE, et al. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. Surv Ophthalmol. 2001;46(1):59–80.
10. Amemiya T, Bhutto IA. Retinal vascular changes and systemic diseases: corrosion cast demonstration. Ital J Anat Embryol. 2001;106(2 Suppl 1):237–44.
11. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA. 2002;287(9):1153–9.
12. Wong TY. Is retinal photography useful in the measurement of stroke risk? Lancet Neurol. 2004;3:179–83.
13. Ikram MK, Witteman JC, Vingerling JR, et al. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. Hypertension. 2006;47(2):189–94.
14. Wong TY, Klein R, Klein BE, et al. Retinal vessel diameters and their associations with age and blood pressure. Invest Ophthalmol Vis Sci. 2003;44(11):4644–50.
15. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 1999;150(3):260–70.
16. Klein R, Klein BE, Moss SE, et al. Retinal vascular caliber in persons with type 2 diabetes: the Wisconsin Epidemiological Study of Diabetic Retinopathy. Ophthalmology. 2006;113(9):1488–98.
17. Wong TY, Shankar A, Klein R, et al. Retinal arteriolar narrowing, hypertension, and subsequent risk of diabetes mellitus. Arch Intern Med. 2005;165(9):1060–5.
18. Edwards MS, Wilson DB, Craven TE, et al. Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the Cardiovascular Health Study. Am J Kidney Dis. 2005;46(2):214–24.
19. Wong TY, Shankar A, Klein R, et al. Retinal vessel diameters and the incidence of gross proteinuria and renal insufficiency in people with type 1 diabetes. Diabetes. 2004;53(1):179–84.
20. Wong TY, Coresh J, Klein R, et al. Retinal microvascular abnormalities and renal dysfunction: the Atherosclerosis Risk in Communities Study. J Am Soc Nephrol. 2004;15(9):2469–76.
21. Wong TY, Sabanayagam C, Shankar A. Retinal microvascular caliber and chronic kidney disease in an Asian population. Am J Epidemiol. 2009;169:625–32.
22. Klein R, Klein BE, Moss SE, et al. Retinal vascular abnormalities in persons with type 1 diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. Ophthalmology. 2003;110(11):2118–25.
23. Marshall SM. Screening for microalbuminuria: which measurement. Diabet Med. 199l;8:706–11.
24. Hoste L, Dubourg L, Selistre L, et al. A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. Nephrol Dial Transplant. 2014;29(5):1082–91.
25. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
26. Witte EC, Lambers Heerspink HJ, de Zeeuw D, et al. First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am Soc Nephrol. 2009;20:436–43.
27. Feldt-Rasmussen B, Borch-Johnsen K, Mathiesen ER. Hypertension in diabetes as related to nephropathy. Early blood pressure changes. Hypertension. 1985;7:1118–20.
28. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39(Supp1 1):S1–S266.
29. Matthew SE, David BW, Timothy EC, et al. Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the Cardiovascular Health Study. Am J Kidney Dis. 2005;46(2):214–24.
30. Klaus PK, Henrik S, Gorm J, et al. New definition of microalbuminuria in hypertensive subjects-association with incident coronary heart disease and death. Hypertension. 2005;46:33–7.
31. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–6.
32. Wong TY, Coresh J, Klein R, Muntner P, Couper DJ, et al. Retinal microvascular abnormalities and renal dysfunction: the Atherosclerosis Risk in Communities Study. J Am Soc Nephrol. 2004;15(9):2469–76.
33. Charumathi S, Anoop S, David K, et al. Retinal microvascular caliber and chronic kidney disease in an Asian population. Am J Epidemiol. 2008;169(5):625–32.
34. Bao SM, Huang W. An epidemiologic study of the relationship between retinal vascular abnormalities and chronic renal disease. Master's thesis. Beijing: Capital Medical University; 2011.
35. Sabanayagam C, Shankar A, Klein BE, et al. Bidirectional association of retinal vessel diameters and estimated GFR decline: the Beaver Dam CKD Study. Am J Kidney Dis. 2011;57(5):682–91.
36. Joanne WYY, Jing X, Ryo K, et al. Retinal arteriolar narrowing and subsequent development of CKD stage 3: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 2011;58(1):39–46.
37. Barr EL, Wong TY, Tapp RJ, et al. AusDiab Steering Committee. Is peripheral neuropathy associated with retinopathy and albuminuria in individuals with impaired glucose metabolism? The 1999–2000 AusDiab. Diabetes Care. 2006;29:1114–6.

38. Huang SR, Zhang XF. Fundus changes in primary hypertension. Ophthalmology. 2010;19(6):368–71.
39. Wong TY, Mitchell P. Hypertensive retinopathy. N Engl Med. 2004;351:2310–7.
40. Nag S, Robertson DM, Dinsdale HB. Morphological changes in spontaneously hypertensive rats. Acta Neuropathol (Berl). 1980;52(1):27–30.
41. Norrelund H, Christensen KL, Samani NJ, et al. Early narrowed afferent arteriole is a contributor to the development of hypertension. Hypertension. 1994;24:301–8.
42. Wang JY. Internal medicine. 2nd ed. Beijing: People's Medical Publishing House; 2010. p. 579–84.
43. Levy BI, Ambrosio G, Pries AR, et al. Microcirculation in hypertension: a new target for treatment? Circulation. 2001;104:735–40.
44. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the atherosclerosis risk in communities study. Ophthalmology. 1999;106:2269–80.
45. Klein R, Klein BE, Moss SE, et al. Hypertension and retinopathy, arteriolar narrowing and arteriovenous nicking in a population. Arch Ophthalmol. 1994;112:92–8.
46. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar diameters and risk for hypertension. Ann Intern Med. 2004;140:248–55.
47. Axel RP, Timothy WS, Peter G. Structural autoregulation of terminal vascular beds: vascular adaptation and development of hypertension. Hypertension. 1999;33:153–61.
48. Leung H, Wang JJ, Rochtchina E, et al. Relationships between age, blood pressure, and retinal vessel diameters in an older population. Invest Ophthalmol Vis Sci. 2003;44:2900–4.
49. Smith W, Wang JJ, Wong TY, et al. Retinal arteriolar narrowing is associated with 5-year incident severe hypertension. The Blue Mountains Eye Study. Hypertension. 2004;44:442–7.
50. Wong TY, Klein R, Sharrett AR, et al. The prevalence and risk factors of retinal microvascular abnormalities in older persons: the Cardiovascular Health Study. Ophthalmology. 2003;110:658–66.
51. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. Br J Ophthalmol. 2002;86:1007–13.
52. Kamran Ikram M, Witteman JCM, Vingerling JR, Breteler MMB, Hofman A, de Jong PTVM. Retinal vessel diameters and risk of hypertension the Rotterdam Study. Hypertension. 2006;47:189–94.
53. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. Neurology. 2006;66(9):1339–43.
54. Wong TY, Shankar A, Klein R, et al. Prospective cohort study of retinal vessel diameters and risk of hypertension. BMJ. 2004;329(7457):79–82.
55. Liang X, Huang W. A survey of the prevalence and risk factors of CKD in Handan, Hebei Province, China. Master's thesis. Beijing: Capital Medical University; 2011.
56. Ding N, Huang W. A discussion on the relationship between retinal blood vessel caliber and hypertension and albuminuria. Master's thesis. Beijing: Capital Medical University; 2012.
57. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med. 2009;361:40–51.
58. Chen HZ. A practical guide to internal medicine. 12th ed. Beijing: People's Medical Publishing House; 2005. p. 1027–34.
59. Wilkinson CP, Ferris FL III, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110:1677–82.
60. 2011 Annual report of Beijing Blood Purification Quality Control and Improvement Center.
61. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984;102:520–6.
62. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984;102:527–32.
63. Klein BE, Moss SE, Klein R, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. Ophthalmology. 1991;98:1261–5.
64. Klein R, Klein BE, Moss SE, et al. The 10-year incidence of renal insufficiency in people with type 1 diabetes. Diabetes Care. 1999;22:743–51.
65. Rema M, Mohan V, Deepa R, et al. Chennai Urban Rural Epidemiology Study-2. Association of carotid intima media thickness and arterial stiffness with diabetic retinopathy: the Chennai Urban Rural Epidemiology Study (CURES-2) 38. Diabetes Care. 2004;27:1962–7.
66. Wong TY, Mohamed Q, Klein R, et al. Do retinopathy signs in non-diabetic individuals predict the subsequent risk of diabetes? Br J Ophthalmol. 2006;90:301–3.
67. Garner A. Histopathology of diabetic retinopathy in man. Eye. 1993;7:250–3.
68. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. JAMA. 2002;287(19):2528–33.
69. Klein R, Marino EK, Kuller LH, et al. The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study. Br J Ophthalmol. 2002;86:84–90.
70. Fan M, Liu G. A preliminary exploration of the correlation between diabetic retinopathy and diabetic nephropathy. Sichuan J Physiol Sci. 2006;28(2):87–9.
71. Vicki HKT, Ellen PKL, Benjamin CYC, et al. Incidence and progression of diabetic retinopathy in Hong Kong Chinese with type 2 diabetes mellitus. J Diabetes Complications. 2009;23:185–93.
72. Boelter MC, Gross JL, Canani LH, et al. Proliferative diabetic retinopathy is associated with microalbuminuria in patients with type 2 diabetes. Braz J Med Biol Res. 2006;39(8):1033–9.
73. Verna P, Duri P. Ischemic retinitis as a result of acute episodic blood loss. Int Ophthalmol. 1998;22:331–3.
74. Klein R, Sharrett AR, Klein BEK, et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes. The Atherosclerosis Risk in Communities Study. Ophthalmology. 2002;109:1225–34.
75. Harris MI, Klein R, Cowie CC, et al. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. Diabetes Care. 1998;21:1230–5.
76. Haffner SM, Fong D, Stern MP, et al. Diabetic retinopathy in Mexican Americans and non-Hispanic whites. Diabetes. 1988;37:878–84.
77. Haffner SM, Hazuda HP, Stern MP. Effect of socioeconomic status on hyperglycaemia and retinopathy levels in Mexican Americans with NIDDM. Diabetes Care. 1989;12:128–34.
78. Zhang L, Krzentowski G, Albert A, et al. Risk of developing retinopathy in Diabetes Control and Complications Trial type 1 diabetic patients with good or poor metabolic control. Diabetes Care. 2001;24:1275–9.
79. Matthews DR, Stratton IM, Aldington SJ, et al. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol. 2004;122:1631–40.
80. Klein R, Klein BE, Moss SE. The relation of systemic hypertension to changes in the retinal vasculature: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 1997;95:329–48.

81. Cugati S, Cikamatana L, Wang JJ, et al. Five-year incidence and progression of vascular retinopathy in persons without diabetes: the Blue Mountains Eye Study. Eye. 2005;20(11):1239–45.
82. Yu T, Mitchell P, Berry G, et al. Retinopathy in older persons without diabetes and its relationship to hypertension. Arch Ophthalmol. 1998;116:83–9.
83. Wong TY, Barr EL, Tapp RJ, et al. Retinopathy in persons with impaired glucose metabolism: the Australian Diabetes Obesity and Lifestyle (AusDiab) study. Am J Ophthalmol. 2005;140:1157–9.
84. Wong TY, Klein R, Duncan BB, et al. Racial differences in the prevalence of hypertensive retinopathy. Hypertension. 2003;41:1086–91.
85. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet. 2001;358:1134–40.
86. Wong TY, Klein R, Sharrett AR, et al., ARIC Investigators. Atherosclerosis Risk in Communities Study. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA. 2002;288:67–74.
87. Mitchell P, Wang JJ, Wong TY, et al. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology. 2005;65:1005–9.

The Obstructive Sleep Apnea Syndrome and Eye Disorders

27

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27.1 Introduction

Obstructive sleep apnea syndrome (OSAS) is a common type of ENT disease and the most common type of sleep disorder. The disease easily leads to the occurrence of paroxysmal hypoxia in patients with sleep, followed by diseases of multiple systems. In the past, physicians were accustomed to seeing them as two distinct diseases. Careful physicians may notice that some patients with diabetic eye disease complain of poor quality of sleep, so is there a link between the two? How do they relate to systemic diseases? If we think from the perspective of integrated medicine, we can find that, first of all, theoretically, they have similar paths in pathology and physiology. Alternating hypoxia and awakening caused by "snoring" will stimulate the sympathetic nervous system, causing a series of cascade reactions, including neurohumoral regulation disorder. In contrast, the microcirculation system meets the needs of eye tissue metabolism through the nervous, humoral, and metabolic regulation; myogenic regulation; and self-regulation. Second, from the clinical practice point of view, the two have similar comorbid diseases such as diabetes and high blood pressure; and in scientific research practice, some of the clinical studies have verified the relevance of the two types of diseases. Therefore, we can fully understand the disease only through establishing a scientific "integrative" concept, grasping the correct understanding and practicing the concept of development.

All along, people have seen snoring as a healthy and harmless behavior, or even an evidence of "high-quality sleep." But with the deepening of the study of sleep, it has been gradually realized that "snoring" may be a warning the body issues to us. Some kinds of snoring will cause sleepers to wake up frequently at night, seriously affecting the quality of sleep and resulting in excessive sleepiness and loss of vigilance during the day, and they are even associated with the occurrence of a variety of cardiovascular and cerebrovascular diseases, so sleep disease with these kinds of "snoring" as the most common manifestations is classified into the category of sleep disorders, and is the most common disease in the category; it is termed as obstructive sleep apnea syndrome (OSAS). Under physiological status, the maintenance of the upper respiratory tract ventilation function depends on the maintenance of local respiratory muscle tension and synchronous activities [1], but OSAS patients, due to the presence of upper respiratory tract anatomy abnormalities, combined with upper respiratory tract dilator muscle relaxation, neurological disorders, and tension decrease, are prone to localized collapse or even complete occlusion of the upper respiratory tract, limited inspiratory flow, and consequentially hypoxia during sleep. Paroxysmal hypoxia further induces repeated unconscious awakening; the alternating hypoxia and awakening of the tissues will stimulate the sympathetic nervous system, causing a series of cascade reactions [2]. This will destroy the self-regulation and vascular endothelial function of the body's vascular tissues, and ultimately lead to a variety of systemic diseases such as pulmonary hypertension, myocardial infarction, arrhythmia, congestive heart failure, stroke, and vascular disease. Then what effect OSAS will have on the eyes, which are important organs of the body? In this chapter, we detail the various types of ophthalmic diseases that may be associated with OSAS.

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_27

27.2 Obstructive Sleep Apnea Syndrome

People's knowledge of OSAS began in the 1970s, and China's research in related fields started late, with a history of only 20-plus years. At the 2002 meeting in Hangzhou, the Chinese Medical Association of Otorhinolaryngology Branch developed and published the diagnostic criteria and efficacy evaluation criteria for OSAS in China [3], which was revised in 2011 [4]. OSAS is defined therein as apnea and hypopnea caused by collapse and obstruction of airway during sleep, accompanied by snoring, sleep disorder, frequent decrease of oxygen saturation, daytime sleepiness, and other symptoms. Obstructive apnea refers to the absence of airflow through the mouth and nose while the chest and abdominal breathing movements exist during the apnea. Apnea refers to a stop of airflow through the mouth and nose for ≥10 s. Low ventilation (hypoventilation) means that the intensity of respiratory airflow during sleep is more than 50% lower than the basal level and is accompanied by a 4% reduction in arterial oxygen saturation (SaO_2). Apnea-Hypopnea Index (AHI) refers to the number of episodes of apnea and hypopnea per hour in sleep (unit: episodes/h).

The diagnosis criteria of OSAS are as follows: (1) symptoms: patients usually have daytime sleepiness, severe snoring, and repeated apnea during sleep; (2) signs: examination reveals upper airway stenosis factors; (3) polysomnography (PSG) shows more than 30 episodes of apnea and hypopnea, or sleep apnea and hypopnea index ≥5 episodes/h during 7-h sleep every night. Apnea is mainly obstruction based; (4) imaging examination shows abnormal airway structure. OSAS should be differentiated with the following diseases: central sleep apnea syndrome; other diseases with OSAS symptoms, such as hypothyroidism and acromegaly. According to AHI, the severity of OSAS can be divided into mild (AHI = 5–15), moderate (AHI >16–30), and severe (AHI >30). According to the lowest SaO_2, the degree of hypoxemia in OSAS patients was divided into mild (lowest SaO_2 ≥85%), moderate (lowest SaO_2 = 85–80), and severe (lowest SaO_2 <80). In OSAS diagnosis, AHI should be used as the basis for disease severity evaluation, and hypoxemia status should also be indicated, such as "moderate OSAS with mild hypoxemia."

The current treatment of OSAS includes the following categories [4]: (1) etiological treatment: the underlying diseases that cause or aggravate OSAS will be corrected, such as the application of thyroxine for treatment of thyroid dysfunction; (2) general treatment (lifestyle changes): this includes diet and weight control, adequate exercise, alcohol and smoking abstinence, withdrawal of sedative hypnotic drugs and other drugs that may cause or exacerbate OSAS, sleep in the lateral position, etc.; (3) oral appliance treatment: it is for simple snoring and mild OSAHS patients (AHI <15 episodes/h), especially those with mandibular retrusion; (4) noninvasive continuous positive airway pressure (CPAP): it is the preferred treatment for adult OSAS patients; (5) surgical treatment: it is suitable only in cases where surgery can definitely resolve upper airway obstruction.

27.3 Eye Diseases Potentially Associated with OSAS

According to the reports in the literature hitherto, ocular diseases potentially associated with OSAS include floppy eyelid syndrome (FES), noninflammatory ischemic optic neuropathy (NAION), primary open-angle glaucoma (POAG), idiopathic intracranial hypertension (IIH), retinal vein occlusion, and diabetic retinopathy.

The close correlation between OSAS and FES is now widely accepted. It is reported in the literature that the prevalence of OSAS in FES patients can be as high as 90% [5], while the prevalence of FES in patients with OSAS is 25.8%; and in patients with severe OSAS, FES prevalence can be up to 40% [6]. The symptoms and signs of FES patients were significantly improved after CPAP monotherapy, while the FES symptoms may still recur months or even years after eyelid-tightening surgery in patients with both FES and OSAS who did not receive CPAP treatment. This suggests that there is a close relationship between OSAS and FES. Therefore, some scholars have proposed that FES patients should receive sleep-related treatment before surgery [7].

The correlation between OSAS and NAION is also widely supported. The prevalence of OSAS in NAION patients is high, which is about 89%, and the risk correlation between OSAS and NAION was found to be higher than those between them and other common risk factors such as hypertension and diabetes mellitus after statistical analysis of the associated risk factors [8]. The correlation between OSAS and POAG is one of the research hotspots, and it is still controversial. Among the studies of the prevalence of POAG in OSAS patients, five studies' results showed a prevalence of POAG of 5.7–27% in OSAS patients, significantly higher than in the normal population, and the proportion of patients with normal-pressure glaucoma is high in patients with concomitant POAG [9–13]. However, one study showed that the prevalence of POAG in OSAS patients was only 2.2%, suggesting no correlation between OSAS and POAG [14]. Similarly, the results of OSAS prevalence in patients with POAG were also inconsistent. Four studies showed prevalences of OSAS in patients with POAG of 20–55%, significantly higher than in the normal population [9, 10, 12, 15]. All the OSAS diagnoses in the above studies depend on the PSG results. However, a retrospective study found that the prevalence of OSAS in patients with POAG was 1.1%, which is not significantly dif-

ferent from that in the normal population at the same period [13]. Because of the differences in the design and examination methods, it is difficult to compare the results of the trials. Besides, there is literature suggesting a link between OSAS and glaucoma diagnosis indicators. OSAS patients have higher intraocular pressure, and the AHI of OSAS patients is significantly correlated with their intraocular pressure, MD, cup/disk ratio, and RNFL thinning [10]. But Lundmark et al. [16] found that the intraocular pressure declined significantly when the magnitude of chest pressure decrease was increased in an obstructive apnea model established in the normal human body by forming a chest negative pressure through the Muller way. The intraocular pressure decreased significantly at the end of the application of −20 cmH_2O and during the application of −40 cmH_2O.

The correlation between OSAS and optic nerve edema and IIH is also inconclusive. As reported in the literature, OSAS patients have high incidence of optic disc edema-related symptoms [17], male IIH patients have increased risk of OSAS [18], IIH patients' optic nerve edema improved after CPAP treatment [19], and the disc edema of patients with concomitant optic nerve edema and OSAS also improved after tracheal incision [20]. The above studies all support the correlation between OSAS and optic nerve edema and IIH, but some researchers found that the incidence of optic disc edema was not significantly increased in OSAS patients [21] and OSAS prevalence was not significantly increased in IIH patients [22], so they do not think that such correlation exists.

We also studied the relationship between OSAS and the prevalence of glaucoma and its impact on patients' vision field and RNFL. According to AHI, the subjects were divided into normal, mild, moderate, and severe groups. The results showed that the prevalence of POAG in OSAS patients was 5.49%. The mean IOP of patients with OSAS was higher than that of the normal group. OSAS could impair the visual field of the patients. The MD value of the severe group was significantly lower than that of the normal and moderate groups and was significantly correlated with ODI. In terms of RNFL, the nasal RNFL of patients with OSAS was significantly thinner, while the inferior RNFL changes were more complex, with mild and moderate OSAS patients' inferior RNFL thinner and severe patients' inferior RNFL not significantly different from the normal group but significantly thicker than that of the moderate group. In view of the different trends of inferior RNFL in the severe group, we further divided the severe group into normal RNFL, thinning RNFL, and thickening RNFL according to the change of the inferior RNFL and derived the intracranial pressure levels of the patients according to formula. After analysis, we found that there was no significant difference in intraocular pressure between the groups, and the intracranial pressure level was significantly decreased in the thinning group and significantly increased in the thickening group. Our results suggest that the high degree of hypoxia in severe OSAS patients damages the systemic vascular system, resulting in blood supply and pressure disorders around the optic nerve. The trans-lamina cribrosa pressure gradient is broken as a result, affecting the axoplasmic flow transport and eventually leading to different changes in RNFL [23].

With the expansion of the OSAS study, there have been recent literatures suggesting that OSAS may be a risk factor for retinal vein occlusion [24]. At the same time, OSAS can affect the level of glucose metabolism in patients and is related with the occurrence of diabetic retinopathy, and AHI value is significantly related with the severity of retinal microvascular disease [25]. Macular edema was reduced in patients with concomitant diabetic retinopathy and OSAS after CPAP treatment [26].

27.4 Mechanism of OSAS Causing Damages to the Eyes

The intermittent hypoxia and reperfusion in OSAS patients increased the body's inflammatory load and oxygen demand. OSAS patients have more oxidative by-products in their body, and xanthine oxidase (xanthine oxidase) and lipid peroxide (lipid peroxides) levels decrease, damaging the body's antioxidant capacity [27]. Inflammatory factors such as tumor necrosis factor-α and nuclear factor kappaB also increased [28]. These inflammatory factors and oxygen overload can damage ganglion cells and cause elevated intracranial pressure [29]. In addition, OSAS patients' sympathetic nervous system is abnormally excited, and the catecholamine content in the body fluids and urine was significantly increased [30], which, in combination with the release of abnormal inflammatory factors and increased oxygen load, damages the vascular endothelial cell function, so the self-regulation function of the vascular system supplying the eyes is disrupted. It is reported in the literature that OSAS patients experienced abnormal blood pressure drops at night [31], and the body was in the state of hypercapnia, further increasing the complexity of vascular regulation. In general, when hypoxia occurs during sleep, peripheral small vessels will constrict and vital organs such as heart and brain will have increased blood supply [32, 33]. In theory, the supply to the optic nerve at this stage should be increased, but in fact, due to high ventilation after hypoxia, the peripheral blood vessels will be dilated due to relatively low levels of carbonation [34, 35], so the vascular regulation process is more complicated in OSAS patients. The self-regulation function of the vascular system supplying the eyes is weakened, so when the blood supply in the brain drops the blood vessels supplying the brain may "steal blood" from the ophthalmic artery, further aggravating the eye blood supply [34].

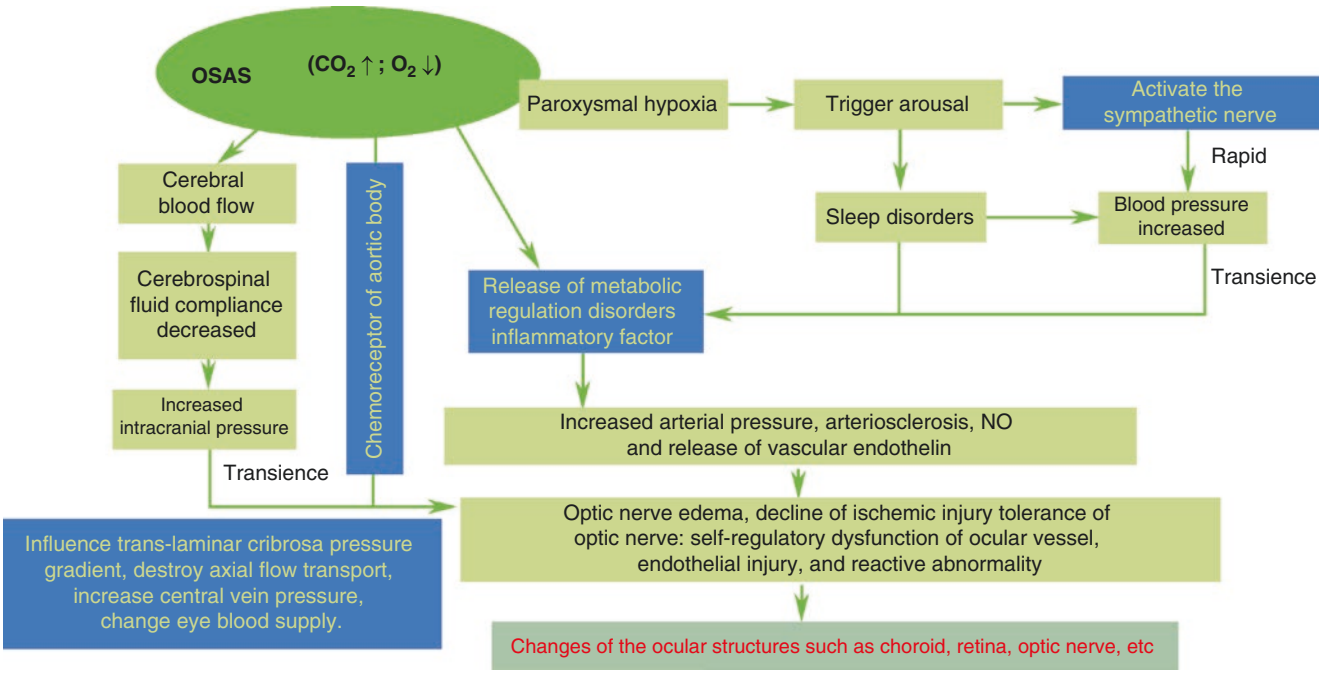

Fig. 27.1 Schematic diagram of the patient's ocular damage mechanism in OSAS

Based on the above results, it is speculated that OSAS patients, due to paroxysmal hypoxia and triggered awakening at night, have decreased oxygen saturation and increased carbon dioxide partial pressure, which stimulates the sympathetic nervous system to increase the patients' blood pressure and cause abnormal blood distribution, leaving cerebral blood flow increased. Hypoxia results in abnormal release of inflammatory factors, arterial pressure increase, and atherosclerosis, which promotes the release of nitric oxide and endothelin; meanwhile, it stimulates aortic chemoreceptors. As a result, optic nerve edema occurs; optic nerve's tolerance to ischemic damage decreases; the self-regulation function, endothelium, and reactivity of the blood vessels supplying the eyes are damaged; and the trans-lamina cribrosa blood supply and pressure balance are broken, which ultimately leads to the impairment of the retina, choroid, and optic nerve and other parts of the eye (Fig. 27.1).

References

1. Strollo PJ Jr, Rogers RM. Current concepts: obstructive sleep apnea. N Engl J Med. 1996;334(2):99–104.
2. Fletcher EC. Sympathetic overactivity in the etiology of hypertension of obstructive sleep apnea. Sleep. 2003;26(1):15–9.
3. Otolaryngology Branch of Chinese Medical Association, Editorial Board of Chinese Journal of Otorhinolaryngology. Diagnosis criteria and efficacy evaluation criteria for obstructive sleep apnea-hypopnea syndrome and the indications of uvulopalatopharyngoplasty (Hangzhou). Chin J Otorhinolaryngol. 2002;37(6):403–4.
4. Sleep-Disordered Breathing Team, Respirology Branch of Chinese Medical Association. Guidelines for diagnosis and treatment of obstructive sleep apnea hypopnea syndrome (2011 revision). Chin J Tuberc Respir Dis. 2012;35(1):9–12.
5. Acar M, Firat H, Acar U, et al. Ocular surface assessment in patients with obstructive sleep apnea-hypopnea syndrome. Sleep Breath. 2013;17(2):583–8.
6. Chambe J, Laib S, Hubbard J, et al. Floppy eyelid syndrome is associated with obstructive sleep apnoea: a prospective study on 127 patients. J Sleep Res. 2012;21(3):308–15.
7. McNab AA. The eye and sleep. Clin Exp Ophthalmol. 2005;33(2):117–25.
8. Palombi K, Renard E, Levy P, et al. Non-arteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. Br J Ophthalmol. 2006;90(7):879–82.
9. Mojon DS, Hess CW, Goldblum D, et al. High prevalence of glaucoma in patients with sleep apnea syndrome. Ophthalmology. 1999;106:1009–12.
10. Sergi M, Salerno DE, Rizzi M, et al. Prevalence of normal tension glaucoma in obstructive sleep apnea syndrome patients. J Glaucoma. 2007;16:42–6.
11. Lin PW, Friedman MW, Lin HC, et al. Normal tension glaucoma in patients with obstructive sleep apnea/hypopnea syndrome. J Glaucoma. 2011;20:553–8.
12. Bendel RE, Kaplan J, Heckman M, et al. Prevalence of glaucoma in patients with obstructive sleep apnoea—a cross-sectional case series. Eye (Lond). 2008;22:1105–9.
13. Karakucuk S, Goktas S, Aksu M, et al. Ocular blood flow in patients with obstructive sleep apnea syndrome (OSAS). Graefes Arch Clin Exp Ophthalmol. 2008;246:129–34.
14. Geyer O, Cohen N, Segev E, et al. The prevalence of glaucoma in patients with sleep apnea syndrome: same as in the general population. Am J Ophthalmol. 2003;136:1093–6.
15. Lin PW, Friedman MW, Lin HC, Chang HW, Wilson M, Lin MC. Normal tension glaucoma in patients with obstructive sleep apnea/hypopnea syndrome. J Glaucoma. 2011;20:553–8.

16. Lungmark PO, Trope GE, Flanagan JG. The effect of simulated obstructive apnoea on intraocular and pulsatile ocular blood flow in healthy young adults. Br J Ophthalmol. 2003;87(11):1363–9.
17. Javaheri S, Qureshi Z, Golnik K. Resolution of papilledema associated with OSA treatment. J Clin Sleep Med. 2011;7:399–400.
18. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. Arch Ophthalmol. 2000;118:1626–30.
19. Thurtell MJ, Bruce BB, Rye DB, Newman NJ, Biousse V. The Berlin questionnaire screens for obstructive sleep apnea in idiopathic intracranial hypertension. J Neuroophthalmol. 2011;31:316–9.
20. Fraser JA, Bruce BB, Rucker J, et al. Risk factors for idiopathic intracranial hypertension in men: a case-control study. J Neurol Sci. 2010;290:86–9.
21. Peter L, Jacob M, Krolak-Salmon P, et al. Prevalence of papilloedema in patients with sleep apnoea syndrome: a prospective study. J Sleep Res. 2007;16:313–8.
22. Thurtell MJ, Trotti LM, Bixler EO, et al. Obstructive sleep apnea in idiopathic intracranial hypertension: comparison with matched population data. J Neurol. 2013;260:1748–51.
23. Xin C, Wang L, Zhang W, Wang J. Changes of visual field and optic nerve fiber layer in patient with OSAS. Sleep Breath. 2015;19:129–34. [Epub ahead of print].
24. Leroux les Jardins G, Glacet-Bernard A, Lasry S, Housset B, Coscas G, Soubrane G. [Retinal vein occlusion and obstructive sleep apnea syndrome]. J Fr Ophthalmol. 2009;32:420–4.
25. Kosseifi S, Bailey B, Price R, Roy TM, Byrd RP Jr, Peiris AN. The association between obstructive sleep apnea syndrome and microvascular complications in well-controlled diabetic patients. Mil Med. 2010;175(11):913–6.
26. Mason RH, Kiire CA, Groves DC, et al. Visual improvement following continuous positive airway pressure therapy in diabetic subjects with clinically significant macular oedema and obstructive sleep apnoea: proof of principle study. Respiration. 2012;84:275–82.
27. Ramar K, Caples S. Vascular changes, cardiovascular disease and obstructive sleep apnea. Future Cardiol. 2011;7:241–9.
28. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnoea syndrome. Circulation. 2005;112:2660–7.
29. Liu Q, Ju WK, Crowston JG, et al. Oxidative stress is an early event in hydrostatic pressure induced retinal ganglion cell damage. Invest Ophthalmol Vis Sci. 2007;48:4580–9.
30. Fletcher EC, Miller J, Schaaf JW, Fletcher JG. Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. Sleep. 1987;10:35–44.
31. Caprioli J, Coleman AL. Perspective: blood pressure, perfusion pressure, and glaucoma. Am J Ophthalmol. 2010;149:704–12.
32. Mojon DS, Mathis J, Zulauf M, et al. Optic neuropathy associated with sleep apnea syndrome. Ophthalmology. 1998;105:874–7.
33. Hosking SL, Evans DW, Embleton SJ, et al. Hypercapnia invokes an acute loss of contrast sensitivity in untreated glaucoma patients. Br J Ophthalmol. 2001;85:1352–6.
34. Hosking SL, Harris A, Chung HS, et al. Ocular haemodynamic responses to induced hypercapnia and hyperoxia in glaucoma. Br J Ophthalmol. 2004;88:406–11.
35. Evans DW, Harris A, Garrett M, et al. Glaucoma patients demonstrate faulty autoregulation of ocular blood flow during posture change. Br J Ophthalmol. 1999;83:809–13.

The Hematology and Eye Disease

28

Liqiang Wei, Jingwen Wang, and Weihong Yu

28.1 Introduction

Blood diseases are diseases that arise spontaneously in the hematopoietic system or affect the hematopoietic system and are accompanied by abnormal blood changes. They include erythrocyte diseases, granulocyte diseases, lymphatic diseases, plasma cell diseases, myeloproliferative diseases, bleeding, thrombotic diseases, etc. Blood diseases can involve various systems and organs of the body. Their early manifestations are often not typical. Most patients with hematological disease first visit in other departments, which leads to misdiagnosis and missed diagnosis. It is reported that about 90% of blood diseases will involve the eyes, but in clinical practice ophthalmologists pay little attention to ischemic eye diseases caused by vascular diseases. If we re-examine the relationship between blood diseases and eye diseases from the perspective of integrated medicine, we can find that eye diseases have the characteristics reflecting the abnormal changes of the blood components: (1) changes in blood components can cause changes in the tone of blood vessels, and thus may cause tissue color or tone abnormalities, such as pale conjunctiva caused by anemia, yellow scleral caused by hemolytic jaundice, and cobalt blue sclera caused by iron-deficiency anemia; (2) ischemia is often accompanied by changes in bleeding, which is mainly due to the destruction of coagulation balance. The pathologic essence of tumor determines that it has the following characteristics: (a) atypical; (b) able to growth; (c) able to diffuse; and (d) able to infiltrate and metastasize (as with malignant tumor). The latter three represent the main causes of tumor damage to tissues and organs. Therefore, eye tumors that have their origins in the hematopoietic system usually have the features of the two. Following the concept of integrated medicine, we should, in clinical practice, have the holistic treatment concept of "holistic analysis and systemic balance" and work with blood department in close cooperation in diagnosis and treatment. We should be concerned about not only the visual impairment caused by blood disease itself, but also the side effects of treatment.

Blood diseases can involve various systems and organs of the body. Their early manifestations are often not typical. Clinically, the vast majority of patients with blood disease are not first received by the hematology department but referred to the hematology department for further diagnosis and treatment by other departments suspecting a blood disease, so they are often misdiagnosed or missed. The eyes are very sensitive sensory organs and their structure is complex and delicate. When they are involved by a blood disease, a variety of eye abnormalities can appear. Some patients seek treatment in the ophthalmology department because of eye discomfort. Therefore, ophthalmologists need to be familiar with the common manifestations of blood diseases to reduce misdiagnosis and missed diagnosis. This chapter focuses on the abnormal ocular manifestations of blood diseases.

28.2 A Brief Introduction on Blood System Diseases

Blood system diseases are diseases that arise spontaneously in or involve mainly blood and hematopoietic organs. They include red cell diseases, granulocyte diseases, lymph diseases, plasma cell diseases, myeloproliferative diseases, bleeding, thrombotic diseases, etc. As the circulating blood reaches all parts of the body, patients with hematological diseases will experience some specific and nonspecific eye abnormalities.

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_28

28.3 The Common Symptoms of Blood System Diseases

Common manifestations of blood system diseases are anemia, infectious fever, infiltration, bleeding, jaundice, etc., and there are also some corresponding ocular manifestations clinically. It is reported that up to 90% of blood disease patients will experience a variety of eye abnormalities, and the most frequently involved parts are the conjunctiva and retina, but most patients have no obvious subjective symptoms [1].

1. Anemia

   The most specific sign is pale palpebral conjunctiva. Severe anemia can cause blurred vision, vision loss, and pale fundus upon fundoscopy, and there may be ischemic optic neuropathy manifestations. In addition, the sclera of patients with iron-deficiency anemia is cobalt blue.
2. Infectious fever

   Blood disease patients often have blood cells that are abnormal in quality and/or quantity, and have immune deficiency, so they are susceptible to a variety of infectious diseases. Eye infections are not uncommon. Common eye infections include periocular skin and soft-tissue infections, and orbital inflammation may occur in severe cases, manifesting as local infections and symptoms of systemic infective intoxication.
3. Infiltration

   Lymphoma, leukemia, and plasma cell diseases are common blood system malignancies. The tumor cells will infiltrate everywhere of the body and often result in local occupying lesions and exudative vascular lesions. When the appendages of the eye are involved, masses will appear in the periocular tissues and appendages. When the masses compress the eyeball, increased intraocular pressure, limited eye movement, proptosis, vision loss, and so on will occur. The lesions can involve a single eye or both eyes. When the fundus blood vessels are involved, exudation, bleeding, and even retinal detachment can occur.
4. Bleeding

   Platelet reduction or dysfunction, coagulation factor abnormalities, etc. can all lead to bleeding from systemic skin and mucous membranes and deep tissues and organs. Common ocular manifestations include periocular skin ecchymosis, hematoma, subconjunctival hemorrhage, fundus hemorrhage, vitreous hemorrhage, hematocele, orbital soft-tissue hematoma, and so on.
5. Jaundice

   The specific sign is yellow scleral. Because bilirubin and scleral tissue have high affinity, scleral yellowing occurs first during jaundice, which will resolve after treatment produces improvement. Jaundice associated with blood disease is hemolytic jaundice, often accompanied by anemia, and pale palpebral conjunctiva is also very obvious.
6. Masquerade Syndrome

   It mainly refers to the neoplastic diseases of the eye which have the characteristics of eye inflammation. Clinically typical examples include retinoblastoma, intraocular and central nervous system lymphoma, uveal melanoma, intravascular metastases of malignancies, and clinical syndromes caused by retinal detachment. Possible manifestations are retinal nodules, vitreous opacities, retina or subretinal masses, anterior empyema, etc. Malignant tumors of the blood system, such as various types of leukemia, lymphoma, and plasma cell tumor, can present as masquerade syndrome when involving the eyes [2].

28.4 Ocular Manifestations of Leukemia

Leukemia is a malignant clonal disease originating from hematopoietic stem cells, mainly including acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, and so on. It is reported that about half of the patients have leukemia-related ocular abnormalities at the first visit [3]. Ocular manifestations of leukemia mainly include vascular stasis caused by hyperleukocytosis, bleeding caused by thrombocytopenia, tissue infiltration by leukemia cells, infections caused by immunodeficiency, etc. [4, 5].

1. Fundus hemorrhage: It often involves both eyes, manifesting as large sheet-shaped hemorrhage from the fundus. It is difficult to explain this with local lesions with the eye. The typical manifestation is the presence of white spots (Roth spots) at the center of the retinal hemorrhage spots. The main causes are leukemia cell infiltration, thrombocytopenia, or coagulation factor abnormalities.
2. Subconjunctival hemorrhage: The typical cases are bilateral subconjunctival hemorrhage. It is related with the degree of reduction of platelets.
3. Vascular occlusion of the fundus: The count of white blood cells in the peripheral blood usually increases by tens of folds in leukemia, which easily leads to vascular stasis. Possible manifestations include obstruction of the fundus arteries and veins, often combined with bleeding.
4. Chloroma: It is also called myeloid sarcoma. Some patients with acute myeloid leukemia also have myeloid sarcoma, and sometimes myeloid sarcoma can also exist alone. Leukemia cells infiltrate soft tissue, forming local space-

occupying lesions in the tissue. This often occurs in the face, manifesting as periocular, orbital space-occupying lesions, space-occupying lesions of the appendages, and oppression of the eye bulb. Chloroma is significantly more common in children with acute myeloid leukemia than in adults with acute myeloid leukemia (Fig. 28.1).

5. Ocular manifestations of increased intracranial pressure: Leukemia patients, especially acute lymphoblastic leukemia patients, are prone to experience central nervous system violations during the remission of the disease, which can involve the cerebrospinal membrane and/or brain parenchyma, causing manifestations of increased intracranial pressure such as disc edema and increased intraocular pressure.

Some scholars classified the ocular manifestations of leukemia into leukemia-specific lesions, leukemia-related injury, and iatrogenic injury. A report described the detailed manifestations and occurrences in 180 patients [6]:

1. Leukemia-specific ocular damage is caused by the infiltration of the structural components of the eye by leukemia cells, mainly including Roth spots, orbital infiltration, optic disc edema, leukemic anterior chamber empyema, optic nerve infiltration, retinal infiltration, and vitreous opacity pale optic papilla. The total incidence of leukemia-specific ocular damage is 16.1% in leukemia patients, and the most common damages are Roth spots, orbital infiltration, and optic disc edema.
2. Leukemia-related ocular damage is caused by the complications of leukemia, mainly including retinal hemorrhage, vascular obstruction, keratitis, blepharitis, subconjunctival hemorrhage, eyelid edema, and conjunctival hyperemia. The total incidence of leukemia-related ocular damage in leukemia patients is 36.6%.
3. Iatrogenic ocular damage is caused by chemotherapy, mainly including atrophy of the choroid and retina, ptosis, vision field reduction, and optic atrophy; total incidence of iatrogenic ocular damage in leukemia patients is 5.5%.

To treat the eye abnormalities of leukemia patients, the method is mainly to treat primary leukemia, that is, combination chemotherapy. For central nervous system leukemia, intrathecal chemotherapy drugs can be given. For ocular myeloid sarcoma, local radiotherapy can be given as necessary in addition to combination chemotherapy.

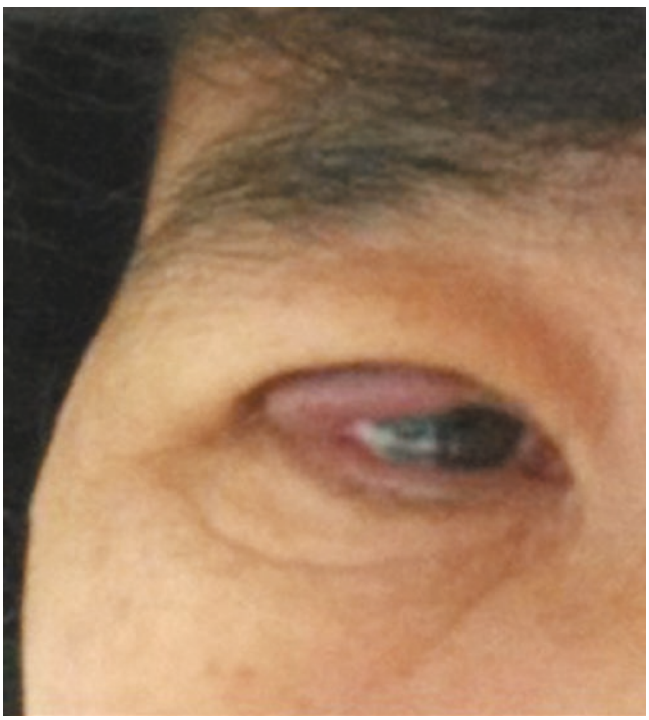

Fig. 28.1 The soft-tissue hyperplasia in upper right eyelid combined with cutaneous tubercle diagnosed as granulocyte sarcoma after biopsy in limbs was found in a patient with relapsed acute myeloid leukemia, and then the cutaneous tubercle and upper right eyelid hyperplasia disappeared after chemotherapy

28.5 Lymphoma Involving the Eyes

Lymphoma is a malignant tumor originating in lymphoid tissue, divided into Hodgkin's lymphoma and non-Hodgkin's lymphoma. The 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues divides lymphoma into more than 50 subtypes, covering more than 90 disease names. Ocular lymphoma is divided into intraocular lymphoma and adnexal lymphoma, with the latter far more common than the former. Its main manifestations are presence of space-occupying lesions in the eyeball and eye appendages (Figs. 28.2, 28.3, and 28.4). Its CT feature is soft-tissue density shadows, and its possible enhanced MRI features include varying degrees of enhancement of tissue signals, unclear lesion boundary, and involvement of periocular soft tissue, eyelid, conjunctiva, lacrimal gland, orbit, and even the inside of the eyeball. Its manifestation on PET/CT is increased metabolic activity at the lesion site [7]. Its clinical manifestations include periocular and adnexal masses, which compress the eyeball and cause proptosis, diplopia, increased intraocular pressure, etc.; intraocular lesions will seriously affect the vision, or even lead to blindness.

The lymphoma that involves the eye appendages most frequently is extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), followed by diffuse large B-cell lymphoma, and T-cell lymphoma rarely involves the eye appendages. Adnexal lymphoma can present as "masquerade syndrome." Ferry et al. retrospectively ana-

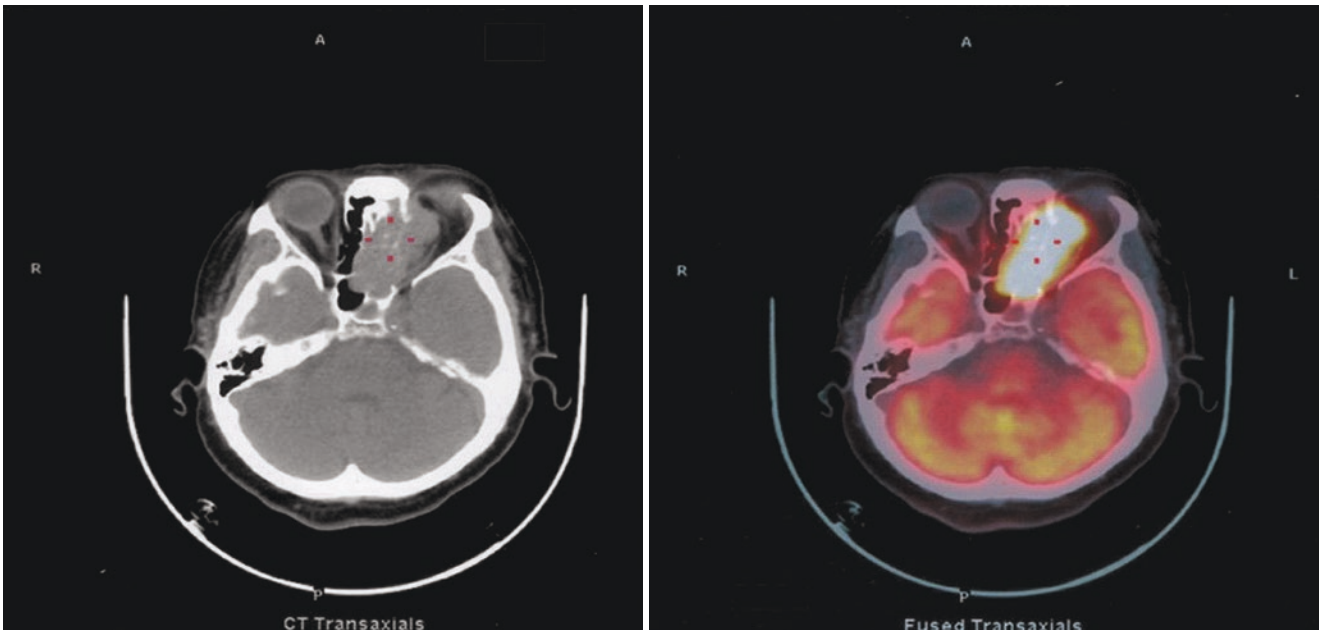

Fig. 28.2 PET/CT shows that the soft tissue-occupying lesion with elevated metabolic activity in left nasopharynx apex has penetrated into the eye, SUVmax36. The pathological diagnosis was Nk/t cell lymphoma outside nasal nodules

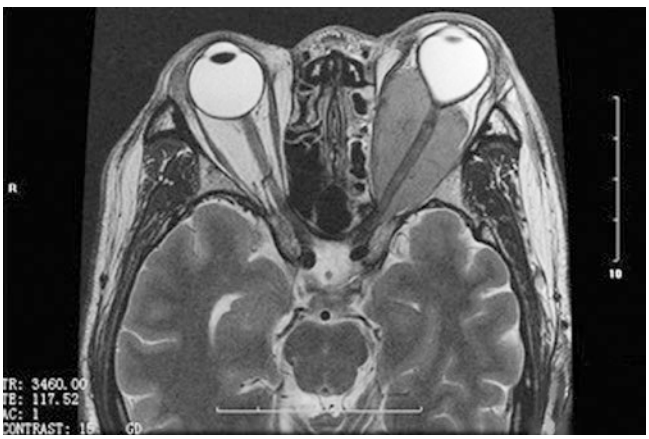

Fig. 28.3 MRI shows left-eye protrusion and abnormal soft tissue signal in left orbit; the pathological diagnosis was B-cell lymphoma in the outer margin of mucosa-associated lymphoid tissue junction

lyzed 353 cases of adnexal lymphoma, and the most common type of lymphoma is the marginal zone lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia, and the parts involved most frequently are orbital soft tissue, conjunctiva, lacrimal gland, etc. [8].

The treatment regimen for adnexal lymphoma is mainly based on the classification and staging of the lymphoma. Invasive lymphoma should be treated with combination chemotherapy or immunotherapy. MALT lymphoma that shows no visible lesion upon imaging after resection can be followed up until the disease progresses when treatment should be initiated. MALT lymphoma that still shows visible lesion upon imaging after resection can be treated with radiotherapy or chemotherapy. A study compared the adverse reactions of the eyes after radiotherapy and/or chemotherapy for adnexal MALT lymphoma in 24 cases, and the complete response rates of radiotherapy, chemotherapy, and radiotherapy + chemotherapy were all 100%. However, the incidence of adverse eye reactions in radiotherapy (30–40 Gy) patients was significantly higher than in non-radiotherapy patients, which mainly include decreased vision, dry eye, cataract, increased intraocular pressure, retinopathy, blepharitis, etc. (Tables 28.1 and 28.2) [9].

Intraocular lymphoma can occur in various structural components of the eye and is often confirmed during vitrectomy or eyeball enucleation necessitated by progressive vision loss and abnormal eye structure. Retinal/choroidal lymphoma is the most common intraocular lymphoma, of which diffuse large B-cell lymphoma is the most common. Retinal lymphoma is also part of the central nervous system lymphoma [10, 11]. Intraocular lymphoma patients with lesions of other parts of the body should be treated with the regimen for systemic lymphoma. If there is no lesion of other parts of the body, the regimen for the central nervous system lymphoma can be used. Prognosis is related with lymphoma classification and staging.

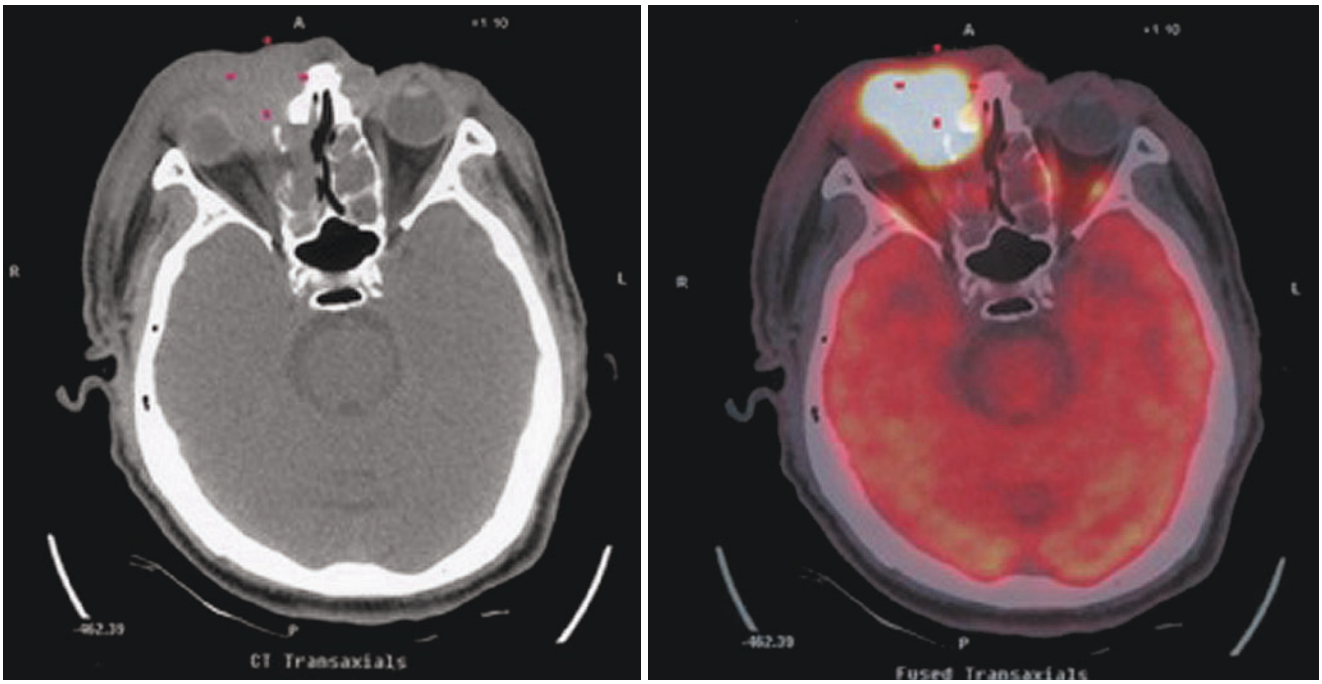

Fig. 28.4 PET/CT shows right facial soft tissue-occupying lesion penetrating into the eye, SUVmax33; the pathological diagnosis was diffuse large B-cell lymphoma

Table 28.1 Basic information of the 353 cases of adnexal lymphoma

Lymphoma type	Cases (%)	Male:female	Average age	Without history of lymphoma (%)	With history of lymphoma (%)
Margin area lymphoma	182 (51.6)	75:107	65	168 (92)	14 (8)
Follicle lymphoma	80 (22.7)	30:50	64	55 (69)	25 (31)
Diffuse large B-cell lymphoma	27 (7.6)	14:13	61	22 (81)	5 (19)
Mantle cell lymphoma	19 (5.4)	13:6	68	7 (37)	12 (63)
Chronic lymphocyte leukemia	13 (3.7)	8:5	70	4 (31)	9 (69)
Others	32 (9.0)	13:19	62	21 (66)	11 (34)
Total	353 (100)	153:200	64	277 (78)	76 (22)

Table 28.2 Distribution of lymphoma in ocular appendages

Lymphoma type	Lacrimal gland ± soft tissue	Conjunctiva ± soft tissue	Soft tissue only	Lacrimal sac ± soft tissue	Mixed type	Both eyes involved (%)
Margin area lymphoma	26	60	84	3	7	20 (11)
Follicle lymphoma	16	24	34	3	3	10 (12.5)
Diffuse large B-cell lymphoma	4	4	16	3	0	3 (11)
Mantle cell lymphoma	3	8	6	0	2	6 (32)
Chronic lymphocyte leukemia	3	2	8	0	0	2 (15)
Others	5	8	18	0	1	5 (16)

28.6 Other Blood Diseases Involving the Eyes

28.6.1 Multiple Myeloma

It is the most common plasma cell malignancy, manifesting as intracranial malignant plasma cell proliferation, increased serum monoclonal immunoglobulin, end-organ damage, etc., and some are also accompanied by extramedullary plasma cell tumor. Ocular manifestations of multiple myeloma are not common. Extramedullary plasmacytoma of the eye can present as periocular and adnexal occupying lesions; when there is hyperimmunoglobulinemia, obstruction of the fundus arteries and veins will occur. There are also rare cases of ocular amyloidosis, manifesting as eyelid stiffness, limited movement, and limited eye movement after eye muscle involvement [12]. Combination chemotherapy should be used for treatment. Local radiotherapy may be considered for ocular adnexal extramedullary plasmacytoma.

28.6.2 Polycythemia Vera

It belongs to myeloproliferative neoplasms, and about 90% of the patients are with JAK-2V617F gene mutation, which is a characteristic gene abnormality. The disease manifests as abnormal proliferation of blood cells uncontrolled by erythropoietin regulation, resulting in significant increase in red blood cell count and hemoglobin concentration in peripheral blood, leaving the blood in a high-viscosity state. About 1/3 of true polycythemia patients are with fundus changes, including blurred optic disc boundary, optic disc edema, tortuous and engorged fundus veins, and fine arteries that reflect light efficiently. Almost all patients have conjunctival and superficial scleral hyperemia in both eyes [13].

28.6.3 Myelodysplastic Syndrome (MDS)

It is a neoplastic disease featuring abnormal hematopoiesis. Its manifestations are hematopoietic dysplasia in the bone marrow and decreased blood cell count in peripheral blood, and anemia, bleeding, infective fever, and other manifestations may be seen clinically. It progresses to acute leukemia in a few months or several years in some patients. It is reported that 19 out of 41 MDS patients (46.3%) are with ocular complications, including 2 cases of corneal ulcer, 5 cases of iridocyclitis, 1 case of vitreous hemorrhage, 10 cases of retinal hemorrhage, 1 case of cotton wool spot, and 2 cases of optic neuritis (some patients have more than one eye complication) [14].

28.7 Other Questions

28.7.1 Visual Abnormalities Caused by Voriconazole

Voriconazole is an antifungal agent commonly used in patients with hematological disease combined with fungal infections. The most common adverse event of this drug is visual impairment. About 30% of subjects in the clinical studies showed visual changes, blurred vision, color perception changes, or photophobia. Long-term visual adverse reactions include optic neuritis and optic disc edema. Visual impairment may be associated with higher plasma concentrations and/or large doses and can fully resolve after discontinuation of voriconazole.

28.7.2 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

It is a rare, reversible neurological disorder that may manifest as seizures, high blood pressure, headache, lethargy, blurred vision, blindness, and other visual and neurological disorders. Leukemia, lymphoma, multiple myeloma, and other patients undergoing combination chemotherapy are at high risk of RPLS. Its manifestations such as visual abnormalities and blindness often make it misdiagnosed [15].

28.8 Summary

The eyes provide us with a window through which we can visually observe the diseases of the whole body, including blood diseases. About 90% of the blood diseases will involve the eyes, so when there occur manifestations that cannot be explained by simple eye disease, internal medicine diseases such as blood diseases should be considered. Severe blood diseases can pose a serious threat to visual function, which is mainly from the blood disease and its progression and partly from the side effects of blood disease treatment. For the treatment of eye diseases caused by blood diseases, close cooperation between hematologists and ophthalmologists is necessary.

References

1. Lang GE, Lang SJ. Ocular findings in hematological disease. Ophthalmology. 2011;108(10):981–93.
2. Gan NY, King LL, Teoh SC. Ocular masquerade syndrome as a herald of progression of acute myelogenous leukemia. Ann Hematol. 2011;90(3):361–2.

3. Schachat AP, Markowitz JA, Guyer DR, et al. Ophthalmic manifestations of leukemia. Arch Ophthalmol. 1989;107:697–700.
4. Wang GH. Ocular signs of acute leukemia. J Ophthalmol Combining Chin Tradit Med West Med. 1998;16(3):177–8.
5. Li XH, Zhang AC, Zhang Y, et al. Ocular manifestations of pediatric acute leukemia. J Appl Clin Pediat. 2001;16(2):122–3.
6. Russo V, Scott IU, Querques G, et al. Orbital and ocular manifestations of acute childhood leukemia: clinical and statistical analysis of 180 patients. Eur J Ophthalmol. 2008;18:619–23.
7. Wei LQ, Wang JW, Feng N, et al. MRI and PET/CT manifestations and clinical analysis of mucosa-associated lymphoid tissue lymphoma of eye adnexa. J Clin Hematol. 2012;25(7):437–9.
8. Ferry JA, Fung CY, Zukerbery L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. Am J Surg Pathol. 2007;31:170–84.
9. Paik J-S, Cho W-K, Lee S-E, et al. Ophthalmologic outcomes after chemotherapy and/or radiotherapy in non-conjunctival ocular adnexal MALT lymphoma. Ann Hematol. 2012;91:1393–401.
10. Davis JL. Intraocular lymphoma: a clinical perspective. Eye. 2013;27:153–62.
11. Raparia K, (Jeff) Chang C-C, Chevez-Barrios P. Intraocular lymphoma. Arch Pathol Lab Med. 2009;133:1233–7.
12. Chin KJ, Kempin S, Milman T, et al. Ocular manifestations of multiple myeloma: three cases and a review of the literature. Optometry. 2011;82:224–30.
13. Dou XY, Du X, Sima J, et al. Analysis of the clinical ocular features of true polycythemia with ocular symptoms as the initial manifestations. Chin J Pract Ophthalmol. 2006;24(6):631–3.
14. Kezuka T, Usui N, Suzuki E, et al. Ocular complications in myelodysplastic syndromes as preleukemic disorders. Jpn J Ophthalmol. 2005;49(5):377–83.
15. Wei LQ, Wang JW, Feng N, et al. Treatment of concomitant multiple myeloma and reversible posterior leukoencephalopathy syndrome with bortezomib plus dexamethasone: a case study and literature review. J Clin Hematol. 2012;25(5):597–600.

Thyroid-Associated Ophthalmopathy

29

Jianmin Ma and Yun Feng

29.1 Summary

Thyroid-associated ophthalmopathy (TAO) has a variety of names previously, such as Graves' ophthalmopathy, ophthalmic Graves' disease, and thyroid-associated ophthalmopathy. Although their names are different, their clinical characteristics are the same, that is, abnormal thyroid endocrine axis (endocrine hormones secreted by the thyroid, pituitary, and hypothalamus or their interactions), and they have similar orbital lesions. Just from an ophthalmologist's point of view, we will have a lot of confusions in clinical practices. For example, how to diagnose and treat the patients who have typical exophthalmos and abnormal eyelids but without any abnormalities upon thyroid function examination and imaging examination. Why have similar treatments produced entirely different effects in different patients having similar clinical manifestations? Why have the eye symptoms and signs worsened after surgery in some patients? For patients with unstable thyroid function and obvious ocular signs, how should we make the choice between ophthalmology and internal medicine? By combining the holistic integrative medicine thinking with the disease characteristics of TAO, we realize that, for some minor TAO with normal thyroid function, we should be wary of the wrong thinking that "laboratory test can replace clinical diagnosis" and should pay attention to the clinical manifestations and characteristic eyelid symptoms, and test results cannot be regarded as the gold standard for diagnosis; when determining the internal medicine regimen for conditions accompanied by abnormal thyroid function, we should, in addition to making active attempts to treat the primary disease, realize that hastily decreasing thyroid function indicators with the internal medicine treatment—iodine treatment may lead to the aggravation of ocular signs; in different individuals and at different stages of the disease, the systemic or ocular changes of TAO will be different, which will make the results difficult to quantify. The principle of individualization should also be followed when standardization of TAO treatment is pursued. Therefore, both the diagnosis and treatment of TAO should be taken into account, and the endocrine and ophthalmic departments should cooperate to make an individualized comprehensive treatment regimen.

29.2 Introduction

Thyroid-associated ophthalmopathy (TAO), is a common orbital disease. The main ocular manifestations include eyelids changes, exophthalmos, eye movement disorders, and other signs. The ocular signs occur at the same time as, before, or after abnormal thyroid function occurs. The thyroid can be hyperfunctional, hypofunctional, or normal, and most of the patients have thyroid endocrine axis dysfunction.

The pathogenesis of TAO is not clear, but it is generally believed that the disease is an autoimmune disease or immune organ disease, associated with the function of endocrine system. And orbital tissue and thyroid may be the attack targets of abnormal immune response. Its pathological features are inflammatory cell infiltration and edema in the early stage, and degeneration and fibrosis of pathological tissue at the advanced stage. Treatment includes systemic treatment and eye treatment [1].

29.3 Clinical Typing

TAO can be divided into two types according to the histological structure, range, and site involved by the lesion. Type I is mainly characterized by retrobulbar adipose tissue and

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_29

connective tissue infiltration, and type II is mainly characterized by extraocular muscle lesions. These two types can coexist or appear alone.

29.4 Clinical Manifestations

29.4.1 Ocular Manifestations

Since 1786 when TAO was reported for the first time, its ocular manifestations have been gradually discovered and described. (1) Eyelid sign: It is an important sign of TAO. Eyelid changes include eyelid edema, eyelid retraction, upper eyelid lag, and reduced blink reflection. The manifestation of eyelid retraction is that the palpebral fissure becomes wider, and part of the scleral tissue exposed, and the eyeballs are at the gazing status. Eyelid retraction was a relatively characteristic change of TAO. Upper eyelids lad refer to the upper eyelids could not move down when the eyeballs turned downward, and the superior scleral was exposed. (2) Exophthalmos: It mostly affects both eyes and one of the eyes may be affected earlier than the other. In a few patients, only one eye is affected. In the early stages of the disease, most of the cases were axial exophthalmos. In the later stages, the eyeball was prominent and fixed at one position because of fibrosis and contracture of the extraocular muscles. Exophthalmos developed faster in patients with thyroid. In some patients, the exophthalmos would aggravate after their hyperthyroidism were controlled. Exophthalmos symptoms and signs sometimes present in some patients after hypothyroidism occurs as a result of hyperthyroidism treatment, indicating that there may be some lag between thyroid dysfunction and ocular signs. (3) Diplopia and eyeball movement disorder: The extraocular muscles may present edema and inflammatory cell infiltration in the early stages. Fibrosis of extraocular muscle may occur in later stages. Multiple extraocular muscles are involved in most of the patients, and their involvements may occur at the same time, or at different times and may be of different severities. Because of the involvement of extraocular muscles, there is a problem of coordination of binocular motion, resulting in double vision and diplopia. Depending on the specific extraocular muscles involved, the affected eyeball may have different eye positions, and can also show a disorder when the eyeball rotates in the opposite direction of the involved muscle movement. (4) Conjunctival and corneal lesions: Orbital soft-tissue edema and increased orbital pressure can worsen the degree of chemosis and conjunctival hyperemia. Severe chemosis may lead to protrusion of the conjunctiva beyond the interpalpebral zone and sandwiching of conjuncitva tissue in the interpalpebral zone, causing dryness and foreign body sensation among other symptoms in the eyes. Hypophasis may lead to exposure keratitis and corneal ulcer, which is accompanied by obvious photophobia and tearing. Corneal perforation, endophthalmitis, and even eyeball atrophy may occur in severe cases. (5) The optic neuropathy: It is secondary changes of TAO and also a serious complication. It is currently believed that optic neuropathy develops as a result of pressure from enlarged extraocular muscles, intraorbital tissue edema, and increased orbital pressure on the optic nerve, and the edematous changes occurring in the tissue near the orbital apex are especially likely to lead to optic neuropathy. Patients may show decreased visual acuity, visual field constriction, or pathological scotoma, and loss of vision, edematous and pale disc, retinal edema and exudation, and tortuous and engorged veins in the fundus may appear in some severe cases [2].

29.4.2 Systemic Manifestations

Systemic manifestations are goiter, reduced tolerance for heat, hidrosis, weight loss, dysphoria, irritability, insomnia, tachycardia, arrhythmia, increased appetite, etc.

29.5 Auxiliary Examinations

29.5.1 Ultrasound Examination

Orbital fat echo enhancement and extraocular muscle thickening are the most common changes upon ultrasound scan in TAO. The typical TAO is bilateral and can involve multiple extraocular muscles. Sometimes it can be seen that both sides are asymmetrical. The orbit of one eye shows significant changes, while the orbit of the other eye only shows slight changes. Even if unilateral orbital disease seems to be present, ultrasonography is often able to detect minor changes in the uninvolved contralateral orbital. It is noteworthy that changes are found in the orbit of only one eye in rare cases.

The thickening of extraocular muscles in TAO often has characteristic morphological changes, but it still needs to be differentiated from some other diseases leading to extraocular muscle lesions (Table 29.1). In most cases, the middle and posterior portions of the extraocular muscles are often involved, but the tendon part of the eye muscle attachment on the eyeball wall is usually not involved. Thickened muscles are moderately or highly echogenic, and their structures are rather irregular. This is caused by edema and inflammatory cells that cause muscle fibers to separate and form large interfaces within the muscle. Other related manifestations included orbital fat and eyelid edema, orbital periosteal thickening, lacrimal gland enlargement, etc.

In cases of apparent edema of the muscle at orbital apex, dilatation of the superior ophthalmic vein or other orbital

Table 29.1 Differential diagnosis of thyroid-related myopathy and other external myopathy

Lesion	Internal echo	Interior structure	Muscle insertion
Thyroid-related myopathy	Middle-high degree	Irregular	Normal
Extraocular myositis	Low degree	Regular	Thickening
Extraocular myopathy caused by tumor	Low-middle degree	Regular	Normal
Extraocular myopathy caused by venous hyperemia	Middle-high degree	Changeable	Normal
Extraocular myopathy caused by hematoma	Low-middle degree	Regular	Changeable

veins and thickening or dilatation of the optic nerve sheath may occur secondary to compression. In some patients with acute TAO, tendon thickening can occur and effusion can be seen in the superior scleral space [3].

29.5.2 CT and MRI

CT scan will reveal hypertrophy of the extraocular muscles and that the lesion mainly involves the muscle belly, which could lead to optic nerve compression in the orbital apex region. MRI examination can more clearly show the morphology of the extraocular muscles and other soft tissues in the orbit. Sometimes, the changes of extraocular muscle signals are helpful in judging the changes of the condition and guiding the treatment. If the extraocular muscles produce long T1 and slightly longer T2 signals, it suggests that the muscles are in the inflammatory edema stage, and the treatment effect is more obvious; if long T1 and short T2 signal are presented, it suggests that muscle fibrosis is more serious, and the treatment effect is poor. In addition, MRI also plays an important role in the differential diagnosis of TAO.

29.5.3 Laboratory Test

Iodine uptake rate of the thyroid is increased, serum levels of T3 and T4 are higher than normal, and serum TSH levels are unstable. A small number of patients can have normal thyroid function test results.

29.6 Diagnosis

Based on the typical clinical manifestations, imaging findings, and laboratory examinations, a definite diagnosis can be made generally. It should be noted that some patients may have normal laboratory tests of thyroid function or have hypothyroidism after treatment for previous hyperthyroidism. For them, as long as there are typical ocular sign, and other similar diseases can be excluded, usually diagnosis can be made.

29.7 Treatment

Treatment includes systemic treatment and eye treatment. Systemic treatment is aimed at correcting abnormal thyroid function. Eye treatment is mainly aimed at correcting exposure keratitis, compression optic neuropathy, and severe congestive orbital disease. The main treatment measures include ocular protective therapy, anti-inflammatory drugs, radiation therapy, and surgical treatment. (1) Eye protective treatment: To prevent exposure keratitis, lubricating eye drops can be used and the palpebral fissure can be covered at night, and tarsorrhaphy may be tried if necessary. (2) Drug therapy: In the acute stage of orbital disease, patients can be treated with glucocorticoids first, and immunosuppressive agents are recommended if glucocorticoid therapy is ineffective. Glucocorticoids can inhibit inflammatory reaction and reduce the orbital tissue edema. The administration pathway and dosage of glucocorticoid administration should be determined according to the specific condition, and the administration pathways generally include intravenous injection, oral administration, intraorbital injection, etc. In the acute stage of the disease, drug treatment may alleviate the edema of the eye tissue, so as to reduce exophthalmos, avoid exposure keratitis, and reduce or prevent the compression of optic neuropathy. For some patients with chronic symptoms, sometimes glucocorticoid treatment is less effective. In order to reduce the side effects of glucocorticoids, glucocorticoid injections can be used locally. They can be injected intraorbitally. For some patients who have no obvious symptoms in the chronic phase, they can be closely followed up. (3) Surgery and radiotherapy: For patients whose exophthalmos has caused corneal damage or serious compressive optic neuropathy, radiotherapy or orbital decompression can be performed to protect and restore the visual function if medication is less effective. In addition, in developed Western countries, in order to improve the patients' exophthalmos symptoms and improve patients' appearance, orbital decompression is usually performed. The occurrence of diplopia or aggravation of diplopia is the most common complication after surgery of orbital decompression. For patients with stable TAO, targeted surgery can be used for treatment according to specific changes in eye conditions. For strabismus patients, topical injection of botulinum toxin A into extraocular muscles or extraocular muscle surgery can be used to correct strabismus. For patients with upper eyelid retraction, surgery for correcting upper eyelid retraction can be used to improve the appearance.

29.8 Complications

29.8.1 Exposure Keratitis

In the acute phase of severe TAO, exophthalmos and hypophasis may lead to corneal exposure and the occurrence of secondary bacterial corneal infection, which results in keratitis, and corneal ulcer or even suppurative endophthalmitis will occur in serious cases. Antibiotic eye drops and drugs to promote corneal epithelial healing should be given for exposure keratitis. Tarsorrhaphy could be tried, and the orbital decompression surgery can be performed if necessary. Active treatment is very important for exposure keratitis; however, it is more important to prevent the occurrence of exposure keratitis. Therefore, rational medication and/or operation is the key to the prevention and treatment of this complication.

29.8.2 Optic Nerve Atrophy

TAO results in edema of orbital tissue and hypertrophy of extraocular muscles. When the lesion is in the vicinity of orbital apex, it is more likely to cause compression optic neuropathy. Acute and subacute TAO patients may develop compressive optic neuropathy, which is especially common in patients with acute-stage TAO. This disease can quickly lead to decreased visual acuity at this stage, and complete loss of vision may be experienced in some severe cases. For the optic neuropathy caused by TAO, a large dose of glucocorticoid can be used for shock treatment. If necessary, orbital decompression may be used to save the visual function of the patients as much as possible.

29.9 Prognosis

The prognosis of TAO is not bad with active and rational treatment. If there are severe complications such as exposure corneal ulcer or optic nerve atrophy occurs, the treatment effect is typically poor and the prognosis is not good.

References

1. Ge J. Ophthalmology. 2nd ed. Beijing: People's Medical Publishing House; 2010.
2. Cui H, Wang NL. Ophthalmology. 3rd ed. Beijing: Peking University Medical Press; 2014.
3. Byrne SF, Green R. Ultrasound of the eye and orbit. Translated by Zhao JL, Ma JM. Beijing: Huaxia Press; 2008.

Virus Infection and Ophthalmic Diseases from the Perspective of Integrated Medicine

30

Yun Feng

30.1 Introduction

We are surrounded by viruses, a common pathogen that can cause all kinds of diseases. Doctors are very familiar with virus infections as it is ubiquitous. Viruses can infect the eye from the ocular surface to the fundus. Herpes zoster virus (HZV) and herpes simplex virus (HSV) infection for instance can cause blepharitis, conjunctivitis, keratitis, scleritis, anterior uveitis, glaucoma, vitritis, and retinal inflammation. On the one hand, the virus attacks the target organ directly and cause serious consequences, such as acute retinal necrosis, and necrotizing keratitis. On the other hand, it can trigger the body's immune response and cause such as keratitis disciformis. Viral eye diseases are difficult to treat. Not only virus infections can happen acutely and can cause serious damage to the eye tissue, but also it can be recurrent. It is a difficult situation that both doctors and patients find hard to deal with. However, if we try to see the problem from the perspective of integrated medicine, we might have more new ideas and new therapy methods.

The human body is made up of different systems. Each system can be specialized into several medical sub-disciplines. Take ophthalmology for instance; sub-disciplines can count up to more than ten. The knowledge of diseases and the treatment are focused on specific areas in this matter. In fact, virus infects most population; the moment to cause diseases depends on certain compromise of immune system of individuals. Viral infection may cause diseases in the human body widely and the pattern of manifestation can be varied. Therefore we should diagnose and treat the disease with the holism concept. For example, intravitreal injection of ganciclovir can be used for retinitis treatment, and can also be used to treat severe corneal keratitis. Clinical knowledge of the virus infection in the eye is usually limited on areas of infection, and treatment is usually with topical medication instead of systemic administration. The doctors are also overcautious because of the fear of side effects. The systemic treatment on severe viral infections is used more effectively by hematologists and dermatologists. This is a practical and effective way to save patients from further damage to the visual function. It can be used to control some severe viral infection diseases in eye. As an old saying goes, "The stones of those hills may be used to polish gems."

Taking oral antiviral drugs to prevent recurrence of viral infection may not be an effective solution for patients who suffered from poor treatment effect and recurrent attacks. Side effects of oral antiviral drugs may occur. In the view of integrated medicine, in fact, it does not mean that the treatment is inefficient, but it should have an integrated method since virus infection is closely related to the patient's immunity. As early as thousands of years ago, the "Inner Canon of Huangdi Neijing, Suwen" mentioned a scientific point of view, " The saint cure the uncured and treat the untreated." Many factors can affect human health, such as lifestyle, genetic, environment, and local quality of medical service. Viral infectious diseases are usually recurrent; therefore care for patients with integrated consideration is needed. There are some risk factors such as late sleep, sleep loss, excessive drinking, smoking, or serious malnutrition. Simple treatment of ophthalmic disorders or prophylactic uses of antiviral drugs are ineffective if the patients do not change their unhealthy lifestyle. Harmful and unhealthy lifestyle that compromises function of immune system can be changed after careful enquiry, which is effective to prevent and treat viral eye diseases. The ancient physician Sun Simiao once said, "The best way of treatment is prevention, the second best way is to treat disease without symptoms the last way is to treat the disease when it breaks out." Doctors should not be satisfied by only successful surgeries or cure of diseases, but should also give patients advices individually, focusing more on prevention methods of the patients with poor immunity. An ancient saying, "The best way of treatment is prevention, to treat the disease before it breaks out and spread, to prevent rather than treat," is a rather up-to-date concept. Local treatment on patients who experience viral disease

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_30

recurrence problems is not sufficient to cure diseases. Integrated treatment with focus on patient general health and lifestyle and long-term advices are needed, to prevent further development of the disease. The integrated medicine is a cross-disciplinary subject and shall always include overall considerations of individuals.

30.2 Viral Infection Diseases

The International Committee on the Taxonomy of Virus (ICTV) from the World Virology Conference which was held in Paris in August 2002 released a No. 7 report, in which more than 3600 viruses were described. The ICTV has identified more than 1200 viruses that are pathogenic to human beings, from which 29 families, 7 subfamilies, and 53 genera were determined. Virus infection is very common, making up to 70–80% of human infectious diseases. The diagnosis and treatment of viral infectious diseases is one of the most challenging topics in the medical field.

Virus is an intracellular microorganism that has a small and simple structure. Virus usually has the following features: (1) simple structure: (a) without cellular structure, (b) with one type of nucleic acid only (DNA or RNA), and (c) without ribosome and complete enzyme system, and without function of energy synthesis and metabolism system; (2) unique reproduction mechanism: (a) without double split and (b) reproduction by replication; and (3) strict intracellular parasitism.

30.3 Knowledge on Ophthalmic Diseases Caused by Viral Infections

Many eye diseases are related to viral infections. Take viral keratitis for example which is commonly known. Acute retinal necrosis (ARN) is usually treated with ganciclovir therapy through intravitreal injection. Nevertheless, many other ocular viral infectious diseases still lack treatment. One of the reasons is that viral infectious eye diseases in patients with normal immune system may be caused by immune reaction with a property of self-recovery; another reason is that ophthalmologists usually lack relevant knowledge on viral infections.

30.3.1 HZV and HSV

HZV and HSV can infect a variety of eye tissues which cause diseases such as blepharitis, conjunctivitis, keratitis, scleritis, anterior uveitis, glaucoma, vitritis, and retinitis. Mother-to-child transmission can cause severe systemic and ocular diseases. Congenital varicella zoster virus or herpes simplex virus retinitis may appear in the birth mother who is known to have varicella zoster or congenital infant herpes simplex virus infection during pregnancy. The most common clinical manifestation of herpes zoster or herpes simplex retinitis is called acute retinal necrosis syndrome. Normally, this is a severe form of uveitis. Retinal vasculitis and retinal necrosis may occur in patients with normal immune function. In the early stage of viral infections, keratic precipitates and vitritis may be observed. The retina usually begins in a week of rapid fusion and results in 10 days, associated with obliterans, vasculitis, and optic neuritis. Retinal detachment usually occurs after a few weeks. The retina may appear in the contralateral eye in more than 1/3 of the patients. Typically, patients with ARN, caused by viruses or herpes simplex viruses, are older than 25 years.

30.3.2 Epstein-Barr Virus (EBV)

Epstein-Barr virus (EBV) can cause choroidal retinitis, which is clinically similar to recurrent multifocal uveitis and multiple white spot syndrome (MEWDS). IgG and IgM antibodies in serum can be detected and monitored. In addition, EB virus-associated antigens can be quantified in serum. Detection of viral DNA in ocular fluid by PCR has been realized. The presence of EBV in the eyes of biopsy specimens was also confirmed by in situ hybridization. In general, EBV-associated retinitis can be self-recovered, but in severe cases acyclovir treatment may be effective. In general, there are limited reports on the treatment of EBV-infected disease, as the EBV-related diseases can be self-recovered.

30.3.3 Human T-Cell Leukemia Virus Type 1 (HTLV-1)

HTLV-1 infection during pregnancy is a risk factor for adult T-cell leukemia and is associated with neurodegenerative diseases known as tropical spastic paraplegia. This virus infection can cause intermediate uveitis. In some populations, infection with HTLV-1 is endemic, as in southwestern Japan. In one study, 0.79% of the population are positive on detection of viral antigens. Ocular manifestations include uveitis and vasculitis. Other manifestations include T-cell conjunctivitis and intraocular lymphoma, interstitial keratitis, Sjogren's syndrome, optic neuritis, choroidal degeneration, and pigmentary degeneration of the retina. Virus DNA testing, including PCR technology, can prove the presence of the HTLV-1 virus. Serum antibodies against HTLV-1 proteins were also used to make the diagnosis of systemic HTLV-1 infection. Intraocular inflammation may be responsive to corticosteroid treatment.

30.3.4 Influenza A Virus

Influenza A virus is a single-stranded RNA virus that causes acute respiratory diseases. The virus carries out the recombination of genomic fragments between viruses, enabling the virus to change its lipid envelope antigen. New outbreaks can happen every year. The infection is spread through respiratory secretions of an acutely infected person. The virus firstly infects epithelial cells in respiratory tract and causes respiratory diseases, accompanied by headache, fever, chills, fatigue, myalgia, coughing, and sore throat. Acute diseases are usually resolved within 2–3 days, and most patients are recovered within 1 week. Ocular complications due to influenza viral infection are iridocyclitis, interstitial keratitis, and inflammation of the lacrimal gland. The posterior segment may manifest macular edema, disappearance of foveal reflexes, darkening of the macula, and optic neuritis. These changes appear to be reversible. There are cases with optic neuropathy and corneal allograft rejection after flu vaccination. Infections of flu viruses usually do not have any sequelae. The posterior segment of influenza A virus infection is reversible and has less effect on vision.

30.3.5 Measles Virus

Measles virus is another RNA virus of paramyxovirus. Infection of the virus can usually be self-recovered and may be associated with subacute sclerosing encephalitis (SSPE). The virus is transferred from nasopharyngeal secretions to the respiratory system or the conjunctiva of susceptible patients. The virus is highly infectious and usually infects child. Congenital infections of the eye cause cataracts and pigmentary degeneration of the retina. The most common ocular infections are keratitis or conjunctivitis which can be self-recovered. Acquired measles viral infections can lead to retinopathy. In the acute phase of retinal involvement, there may be diffuse macular edema, edema of the optic disc, associated small hemorrhages, and macular degeneration. The salt-and-pepper appearance of choroidal retinitis may also occur. Retinal changes associated with SSPE can include macular edema, pigmented epithelial abnormalities, uveitis, macular serous detachment, white infiltration, depigmentation of the retina, and optic neuritis. Macular retinal problems may occur before SSPE detection. Serological test may enable an early identification of SSPE. Fluorescein angiography may show diffuse leakage associated with retinal edema or increased choroidal fluorescence associated with pigmented epithelial diseases. Measles infection without complications does not require treatment. The measles retinopathy may lead to acute blindness within weeks after the onset of measles and is generally alleviated within the next few months. There are no related reports on the treatment of measles-associated retinopathy.

30.3.6 Rubella Virus

The eye manifestations of rubella virus are similar to those of measles virus infection. Congenital rubella retina may be represented by salt-and-pepper fundus appearance. Acquired rubella can manifest in classic rashes and discomfort. Ocular manifestations include conjunctivitis, keratitis, and uveitis. Exudative detachment of the retina is associated with retinal pigment epithelial cells. Reports have shown that some rubella virus may be the reason for Fuchs heterochromic iridocyclitis [1].

30.3.7 Cytomegalovirus (CMV)

CMV is a herpes virus that is widely distributed in the world with high infection rate in human population. In the United States, 80–85% of adults are infected by CMV before 40 years old. In some developing countries, the serum antibody positive rate can be as high as 100%. Although CMV is a common pathogen, systemic infections in patients with normal immune function rarely cause clinical symptoms. The newborn babies and people with low immunity, however, are vulnerable to virus infection and may result in decreased visual acuity due to viral eye diseases. Among the patients with acquired immune deficiency syndrome (AIDS), one out of three has cytomegalovirus retinitis. The knowledge of CMV can be traced back to the last century. In 1956, Margaret Gladys Smith extracted giant cell virus from a dead baby's submandibular gland for the first time. It is an enveloped DNA virus with high specificity in the eosinophilic inclusion body of cytomegalic cell. Diseases caused by CMV are commonly seen in fetus, infants, and immunocompromised individuals. During the primary infection, CMV is disseminated throughout the body in the bloodstream. CMV expresses immune escape genes, evades immune surveillance, and gradually damages neighboring cells. The virus can be reactivated by organ transplantation if the organ is previously infected by CMV. Among the AIDS patients, 1/3 of them have cytomegalovirus retinitis, which is one of the most common and serious opportunistic infections in the advanced period of AIDS. The main causes of vision loss in patients include CMV retinitis showing retinal necrosis and hemorrhage along the temporal retinal vascular; CMV optic neuritis showing optic nerve edematous uplift, blood vessel dilation, and hemorrhage; and CMV retinal vasculitis showing retinal vascular sheath-like changes.

Before the widespread use of highly active antiretroviral therapy for immunocompromised patients, CMV infection has resulted in as many as 2/3 of fundus diseases in patients with AIDS, CMV retinitis mainly. CMV infection in patients with normal immune functions however is more confined to the anterior segment, manifesting CMV uveitis, corneal endotheliitis, etc. [2, 3]. Those are diagnosis and treatment of cytomegalovirus iridocyelitis without retinal necrosis [4]. The findings suggest that more immune-related factors may be involved in the pathogenesis of anterior segment inflammation in CMV-infected patients with normal immune function. Since Koizumi [4] first reported the finding of CMV in the aqueous water of corneal endotheliitis patients in 2006, normal immune function patients with CMV corneal endotheliitis are more commonly reported. Related research articles have been published.

30.4 Looking at Corneal Endotheliitis and Posner-Schlossman Syndrome from the Perspective of Integrative Medicine

Clinically, patients with keratic precipitates (KP) along with high intraocular pressure are often diagnosed with Posner-Schlossman syndrome; when corneal edema is also present, often the corneal endotheliitis is considered as the diagnosis. Increasing evidence suggests that both diseases may be caused by viral infections. In most cases, these two types might be seen either by a corneal or glaucoma specialist. Corneal specialists generally have reached a consensus that corneal endotheliitis is caused by a viral infection; therefore, treatment generally will include systemic antiviral drugs. The intraocular pressure in these patients gradually reduces with control of the viral infection. In fact these two types of diseases can use the same type of clinical treatment, that is, systemic antiviral therapy combined with topical steroids. From the perspective of integrative medicine, these two types of diseases actually belong in the same category, albeit the tissues affected by the virus might be slightly different. Based on embryonic development, the embryo corneal endothelial cells and trabecular meshwork cells are both derived from neural crest cells; therefore the cells may have a similar appearance. Hence when infected by a virus, the cells might be affected at the same time. Some doctors that attempt to treat the high intraocular pressure but ignore the cause of the symptoms are subject to misunderstandings of the Posner-Schlossman syndrome. Some scholars believe that Posner-Schlossman syndrome can be placed into the category of corneal endotheliitis, and adopt systemic antiviral therapy and intravitreal injection therapy.

30.4.1 Corneal Endotheliitis

Corneal endotheliitis, which has been researched extensively in recent years, is an acute nonsuppurative inflammation of the corneal endothelium of unknown etiology. Since its first report in 1982 by Khodadoust and Attarzadeh, corneal endotheliitis has been reported at home and abroad [6]. It is first reported in our country in 1989 by Sun Bingji. This disease has been getting more and more attention from academia in recent years since the cause of the disease is not very clear. It is thought to be related to immune response and viral infection. The infections of human herpes viruses include HSV and varicella zoster virus (VZV), CMV, and EBV, aside from EBV, HSV, VZV, and CMV that can all lead to corneal endotheliitis.

Clinical reports indicate that corneal endotheliitis' main features include corneal deep stroma and corneal endothelial opacity with cortical vesicles and bullae, Descemet's membrane thick folds, and KP. It may also come with iridocyclitis and glaucoma and some mild iridocyclitis. Only few show KP and high intraocular pressure, which resembles Posner-Schlossman syndrome. Sundmacher once classified the syndrome under the viral corneal endotheliitis category. The manifestations of corneal endotheliitis mainly include the following:

1. Corneal edema and CMV infection are the most common linear endotheliitis. Specifically, it is distributed in the peripheral corneal edema. The KP line on the corneal endothelial progresses from the limbus to the center, like a central corneal endothelial transplantation rejection line. Linear corneal endotheliitis may be the most dangerous type because it marks the rapid and massive loss of corneal endothelial cells.
2. Coin-shaped/linear KP: Coin-shaped KP is shown as KP that is annular distributed with a central localized corneal edema, while linear KP is often located on the margin of corneal edema. In a study by Koizumi [4], all of the patients with corneal endotheliitis had coin-shaped KP which led the researcher to believe that the coin-shaped KP is a special sign of the CMS corneal endotheliitis.
3. Elevated intraocular pressure: Patients with CMV corneal endotheliitis won't necessarily experience elevated intraocular pressure. The occurrence of elevated intraocular pressure may be associated with trabecular meshwork disease. After the use of antiviral therapy for CMV, most high intraocular pressure can be controlled.
4. Mild anterior chamber inflammation: The anterior chamber inflammation of CMV corneal keratitis is mild to moderate, and generally there is no anterior chamber flare or posterior iris synechia. For instance, of the 8 subjects in the study by Koizumi, there were 4 cases of anterior

chamber inflammation: 3 cases of 1+ and 1 case of 3+; the remaining four showed no obvious anterior chamber inflammatory response. This phenomenon may be related to the local cellular immunosuppression induced by ACAID.

5. Immune ring formation: In a study by Chee and Jap [5], corneal immune ring occurred in 14.3% of CMV corneal endotheliitis patients. The mechanism remains unclear; the inflammation may be related to the inflammation caused by the CMV presence in the corneal tissue; and the clinical manifestations can disappear after using a small dose of typical steroids and antiretroviral therapy.

Khodadoust and Attarzadeh [6] first reported a finding that one patient with bilateral recurrent corneal edema associated with linear KP is shown to exhibit corneal endothelial rejection. They suggest that it be named autoimmune corneal endothelial disease. However, subsequent observations have shown that some patients with corneal endotheliitis do not respond well to glucocorticoid treatment, suggesting that the cause may be infection. As diagnostic technology advances, more recent studies show that this set of clinical symptoms may be caused by viruses such as CMV. After primary infection, CMV can form latent infection in myeloid precursor cells and be transported to all organs of the body through the blood. Intermittent reactivation of virus comes from activated macrophages or dendritic cells, which can be controlled by virus, specifically CD4+ T-cell and CD8+ T-cell [7] reaction. Koizumi [3] found that corneal endothelial lesions always began to develop from the periphery to the center of the cornea. This suggests that CMV may hide in the cornea tissue such as trabecular meshwork or ciliary body. This theory is well supported by the discovery of bone marrow-derived cells that can migrate to the cornea [8, 9]. Shiraishi found that patients with the CMV corneal endotheliitis have "owl's eye" inclusion body in their cornea, which indicates that CMV can directly attack the corneal endothelium.

Although the pathogenesis of CMV corneal endotheliitis is unclear, the existing evidence suggests that the anterior chamber-associated immune deviation (anterior chamber-associated immune deviation, ACAID CMV) may play a role in CMV corneal endotheliitis. Suzuki and Ohashi [10] predict that when the latent virus is intermittently reactivated, a different number of viruses would spread to the anterior chamber.

Virus particles repeatedly fall off to induce ACAID, which is targeted by viral antigens. Infection occurs when preexisting antibodies do not neutralize the reactivation of the virus. In the surroundings of cellular immunosuppression, the virus can proliferate efficiently in the corneal endothelium. As a recently suggested clinical concept, CMV corneal keratitis lacks sufficient epidemiological data.

Kandori [11] found that in cases with unexplained causes of corneal edema, 24.1% of patients' aqueous humor contained CMV with DNA positive. In corneal endotheliitis cases, patients with a positive aqueous CMV were significantly more susceptible to those with a negative aqueous CMV.

In addition, the existing literature researches are mostly from Japan, Singapore, and other East Asian countries. It cannot be ruled out that the incidence of corneal endotheliitis CMV may be related to racial or genetic susceptibility. Further research needs to verify this.

30.4.2 Posner-Schlossman Syndrome (PSS)

The etiology of PSS remains unknown. The current pathogenesis includes autonomic nerve defects, allergic diseases, viral infection, and trabecular DNA oxidative damage. In the pathogenesis of PSS, the virus is the most important factor driving the inflammation process. Aqueous humor can be tested with polymerase chain reaction (PCR), to confirm that CMV DNA clearly exists in patients with PSS.

Therefore some scholars have adopted systemic and topical antiviral therapies to treat these patients. Topical treatment cannot prevent recurrence. Intravitreal injection treatment can reduce the recurrence rate. Usage of topical anti-glaucoma drugs and antiviral drugs may result in very high recurrence rate.

Chee et al. [5] suggest to take valganciclovir orally for 3 months (response rate 90.9%). However, the recurrence rate was very high (80%) when the therapy stopped. In addition, intravitreal injection of ganciclovir has a 100% recurrence rate. Sobolewska conducted a 13-month study where valganciclovir was taken orally, with a 63.6% response rate (7/11 cases). Conducting cytomegalovirus detection among PSS patients showed that anterior segment inflammation CMV copy number is related to disease features. Kandori showed that CMV viral copy number was significantly associated with repeated episodes and elevated intraocular pressure, but not significantly related to disease type.

These results were confirmed by Miyagana. Distinct corneal endothelial cell losses are correlated to high CMV viral load. PSS in aqueous humor CMV treatment was tested positive. Chee recommended valganciclovir orally for 3 consecutive months (90.9% response rate), after cessation of treatment had a high recurrence rate of 80%. A longer term study suggested a duration evaluation after oral valganciclovir treatment. Sobolewska confirmed a 63.6% response rate (7 versus 11); in 6 cases, the treatment stopped at an average of 14 months.

Ophthalmic HSV or CMV infection may be associated with PSS. However, studies have also shown that polymorphisms in HLA-B and HLA-C genes associated with PSS may confound ophthalmic HSV with CMV infection.

30.5 Exploring the Treatment of Corneal Infectious Diseases with Integrated Medical Methods

30.5.1 Exploring the Treatment of Corneal Infectious Diseases with Integrated Medical Methods

Common types of virus infection include the following: One cell level of infection: (1) Cytotoxic infection: virus in host cell replicates and after maturing releases a large number of progeny viruses, after which the cells are lysed and die. (2) Steady-state infection: the main infection mechanism of enveloped viruses. The release of progeny by budding is relatively slow and the lesion is relatively mild and the cell would not be immediately dissolved and die in a short period of time. It would not destroy the cell, but can create antigen encoded with virus gene on the surface of the cell, making the cell a target cell, and susceptible to immune system's attack. Cell fusion: the formation of multinucleated giant cells, such as measles virus, which have clinical diagnostic significance. (3) Integrated infection: viral gene integrates with host cells. It can chromosomally integrate with host cells, and as the cell divides it transfers to the offspring. On the other hand it can also exist in the form of plasmid cells, which becomes a virus gene carrier. Two (1) dominant infections: when virus within the host cells proliferates, causing massive damage to cells or tissues, or after accumulating substantial toxic products, the body starts to show symptoms. (2) Recessive infection: when virus virulence is weak or the patient has a strong immunity, or when the virus cannot reach the target cell, there will be no clinical symptoms. After the latent infection, the organism may obtain a specific immunity; some become the virus carrier, and have the possibility of expelling toxin, becoming the infection origin. (3) Acute infection: also known as the elimination of pathogenic infection, it has a short incubation period and an acute onset. Starting from the incubation period the host can mobilize specific and nonspecific immune mechanisms to clear the virus. Aside from death cases, in a couple of days or weeks, the patients usually enter recovery period after the virus has been cleared. (4) Persistent infection: the virus persists in the body for months to years, even decades, during which symptoms may occur or may not occur but carries the virus and becomes a source of infection. (5) Chronic infection: in the aftermath of dominant or recessive infection, if virus is not cleared completely, the virus may continue to exist in blood or tissues, and may transmit disease by being expelled by the body, or through blood transfer; the virus can be detected and separated. Clinical symptoms may or may not occur, and the course of infection may last for a couple of months to decades. (6) Slow virus infection: after infection, the virus has a long incubation period, which may last from a couple of months to a couple of decades. The virus cannot be detected, and the body does not show any symptoms. But when the symptoms do occur, it is progressively aggravated or irreversible fatal disease.

After dominant or recessive infection, viral genes are present within certain tissues or cells, but do not produce infectious pathogens. Without clinical symptoms and viral discharge, active viruses cannot be detected by general methods. Under certain conditions, the virus can be activated to replicate an infectious virus, which causes an acute attack along with clinical symptoms. During the dominant seizure phase, virus can be detected. For example: after the HSV-1 infection, the virus will hide in the trigeminal ganglion and the superior cervical ganglion; after VZV infection, the virus will hide in the spinal cord ganglion or the cranial ganglion; when the body is affected by physical, chemical, biological, or environmental impact or decreased immune function, virus would be activated and proliferate, leading to lip and skin herpes.

30.5.2 Effects of Viral Infection on the Immune System

The effect of the viral infection on immunocompetent cells: HIV invading CD4+ T cells, leading to T-cell damage and apoptosis; impaired cell immune function, in conjunction with opportunistic fungal; and viral or parasitic (*Pneumocystis carinii*) infections, or concurrent tumor (for example Kaposi sarcoma) are the main causes of death in AIDS. Viral infection and association with autoimmune disease: viral infection can cause an immune response disorder. The main manifestation is the loss of the cells' recognition of self and non-self antigens, thereby generating an immune response against its own cells or tissues, thereby developing into an autoimmune disease. For example, EB virus infection is associated with systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, autoimmune liver disease, and others.

30.5.3 Status of Antiviral Drugs: The Drugs Cannot Kill the Virus, and the Existing Drugs Can Only Prevent and Treat a Small Number of Viruses

Viruses must be parasitic in the host cells for growth and reproduction, so that antiviral drugs cannot directly kill or destroy the virus body; otherwise it will damage the host cell. Antiviral drugs are designed to inhibit viral reproduc-

tion, protect the host immune system from the invading virus, repair damaged tissue, or ease the condition of the disease to prevent clinical symptoms. Due to the blood-brain barrier, the effect of systemic administration is limited in patients with severe ocular diseases; therefore local treatment is often needed in conjunction.

There have been many studies on intravitreal injection for the treatment of ARN, which can also be an effective treatment for Posner-Schlossman syndrome. In 1987, Henry Kaplan treated an AIDS patient with associated CMV retinitis using 200 μg ganciclovir, with an estimated half-life of about 13.3 h in the vitreous cavity. 62 hours after a single injection of intravitreal ganciclovir, the concentration was still greater than ID50. In 1996, Morlet et al. used large doses of R ganciclovir (2 mg) injected intravitreally for the treatment of seven cases of CMV retinitis. At 24 and 72 h, the vitreous body was sampled for ganciclovir concentration, and the half-life of ganciclovir was estimated to be about 18.3 h. At 7 days, the ganciclovir was eliminated. In addition, this study found no retinal toxicity. Subsequently, large doses of ganciclovir (2 mg) intravitreal injection were successfully used for PORN [12] and acyclovir-resistant ARN [13, 14]. Subsequently, there were reports of moderate dose (1 mg) [15] and greater doses (4 and 5 mg) of intravitreal injection of ganciclovir for the treatment of retinitis [3, 16, 17]. For patients with Posner-Schlossman syndrome and corneal endotheliitis, early intervention with high-dose systemic antiviral drugs along with intravitreal injection can reduce the involvement of corneal endothelial cells, reducing recurrence, and bringing better prognosis. Treatment of Posner-Schlossman syndrome and corneal endotheliitis reflects the methodology of integrative medicine. The intrinsic pathogenic mechanism and the concentration of drug delivery at different periods still need to be further explored. I hope that more doctors can establish this understanding and reduce the recurrence of such patients.

References

1. de Visser L, Braakenburg A, Rothova A, de Boer JH. Rubella virus-associated uveitis: clinical manifestations and visual prognosis. Am J Ophthalmol. 2008;146:292–7.
2. van Boxtel LA, van der Lelij A, van der Meer J, et al. Cytomegalovirus as a cause of anterior uveitis in immunocompetent patients. Ophthalmology. 2007;114:1358 1362.
3. de Schryver I, Rozenberg F, Cassoux N, et al. Diagnosis and treatment of cytomegalovirus iridocyelitis without retinal necrosis. Br J Ophthalmol. 2006;90:852–5.
4. Koizumi N, Suzuki T, Uno T, et al. Cytomegalovirus as an etiologic factor in corneal endotheliitis. Ophthalmology. 2008;115:292–7.
5. Chee SP, Jap A. Immune ring formation associated with cytomegalovirus endotheliitis. Am J Ophthalmol. 2011;152:449–553.
6. Khodadoust AA, Attarzadeh A. Presumed autoimmune corneal endotheliopathy. Am J Ophthalmol. 1982;93:718–22.
7. Carmichael A. Cytomegalovirus and the eye. Eye Reaction (Lond). 2012;26:237–40.
8. Nakamura T, Ishikawa F, Sonoda KH, et al. Characterization and distribution of bone marrow derived cells in mouse cornea. Invest Ophthalmol Vis Sci. 2005;46:497–503.
9. Shiraishi Hiraishi A, Hara Y, Takahashi M, et al. Demonstration of "Owl's" eye morphology by confocal microscopy in a patient with presumed cytomegalovirus corneal endotheliitis. Am J Ophthalmol. 2007;143:715–7.
10. Suzuki T, Ohashi Y. Corneal endotheliitis. Semin Ophthalmol. 2008;23:235–40.
11. Kandofi M, Inoue T, Takamatsu F, et al. Prevalence and features of keratitis with quantitative polymerase chain reaction positive for cytomegalovirus. Ophthalmology. 2010;117:216–22.
12. Meffert SA, Kertes PJ, Lim PL, Conway MD, Peyman GA. Successful treatment of progressive outer retinal necrosis using high-dose intravitreal ganciclovir. Retina. 1997;17(6):560–2.
13. Luu KK, Scott IU, Chaudhry NA, Verm A, Davis JL. Intravitreal antiviral injections as adjunctive therapy in the management of immunocompetent patients with necrotizing herpetic retinopathy. Am J Ophthalmol. 2000;129(6):811–3.
14. Chau TTH, Cassoux N, Bodaghi B, Lehoang P. Successful treatment with combination of systemic antiviral drugs and intravitreal ganciclovir injections in the management of severe necrotizing herpetic retinitis. Ocul Immunol Inflamm. 2003;11(2):141–4.
15. Teoh SC, Ou X, Lim TH. Intravitreal ganciclovir maintenance injection for cytomegalovirus retinitis: efficacy of a low-volume, intermediate-dose regimen. Ophthalmology. 2012;119(3):588–95.
16. Arevalo JF, Garcia RA, Mendoza AJ. High-dose (5000-microg) intravitreal ganciclovir combined with highly active antiretroviral therapy for cytomegalovirus retinitis in HIV-infected patients in Venezuela. Eur J Ophthalmol. 2005;15(5):610–8.
17. Surachatkumtonekul T, Chokephaibulkit K, Vanprapar N, Pamonvaechavan P. Treatment of cytomegalovirus (CMV) retinitis with intravitreous ganciclovir in HIV-infected children. J Med Assoc Thail. 2008;91(3):331–7.

Part VII

The Immune System and Ophthalmopathy

Uveitis and Autoimmune Diseases

31

Meifen Zhang and Bo Wan

31.1 Introduction

The uvea is a common site of ocular immune diseases, due to its features like peripheral immune organ, with abundant vessels and some other ocular antigenic substances such as lens and retinal antigens, which could easily induce the immune-related ocular diseases. Uveitis has many complex symptoms, signs, and causes. Additionally, limitations of understanding of immune diseases could lead to the difficulty of diagnosing. This part introduces the involvement and manifestations of autoimmune diseases on uvea, and correlation between the immune-related manifestations of uveitis and systemic immune diseases. "Get the big picture from small details" to reveal the relationship between eye diseases and immune diseases, as from the perspective of integrative medicine, it would be examined and identified for that whether the uveitis is caused by immune diseases, whether the systemic immune disease affects the eye, what is the relevant diagnostic criteria for immune-related eye diseases, what are the examinations to do, and how to treat. By the establishment of integrative medical thought, broadening minds, understanding the performance of systemic immune diseases, asking history, and checking physical signs, early diagnosis and early treatment could be made, and thus the possibility of misdiagnosis and missed diagnosis of immune-associated uveitis would be decreased.

Uveitis, or inflammation of the uvea, is the major ocular manifestation of multiple systemic autoimmune disorders, which affects both the uveal tract composed of the iris, ciliary body and choroid, and adjacent structures including the retina, retinal vessels, and vitreous body. It is very difficult to diagnose and treat, not only because the etiologies of uveitis still remain unknown at around 50% of patients even by intraocular biopsy which is difficult and limited by the examination method, but also there are no effective and definite therapeutic measures. The causes of uveitis can be organized into infectious, noninfectious, and masquerade syndrome, and most cases of uveitis were noninfectious such as idiopathic, autoimmune, and sympathetic uveitis [1].

Rheumatic immune disease is classified as spondyloarthropathy, connective tissue disorder, systemic vasculitis, metabolism, and degenerative diseases. HLA-B27-associated anterior uveitis (usually the ocular manifestation by ankylosing spondylitis), Behcet's disease (systemic vasculitis), retinal vasculitis (usually the ocular manifestation by systemic lupus erythematosus), and scleritis (usually related to polychondritis) are mainly discussed here [2]. The last part focuses on the differential diagnosis of uveitis and the correct usage of glucocorticoid and immunosuppression.

31.2 Ocular Inflammation and Systemic Autoimmune Disease

31.2.1 HLA-B27-Associated Anterior Uveitis

There are severe clinical symptoms and signs with HLA-B27-associated anterior uveitis, which often recur and may become chronic. Most commonly, anterior segment involvement can be seen in patients with mixed bulbar conjunctival congestion, dense dustlike keratic precipitates (KPs), cell and flare in the anterior chamber, even hypopyon (Fig. 31.1), and fibrinous exudate in the pupil area (Fig. 31.2). Posterior synechiae of iris are frequently present; therefore, mydriasis should be applied actively and thoroughly. Autoimmune diseases associated include ankylosing spondylitis, Reiter syndrome, inflammatory bowel diseases, and psoriatic arthritis. Diagnostic evaluation: Anterior uveitis can be easily diagnosed according to the clinical manifestations. Laboratory examinations:

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_31

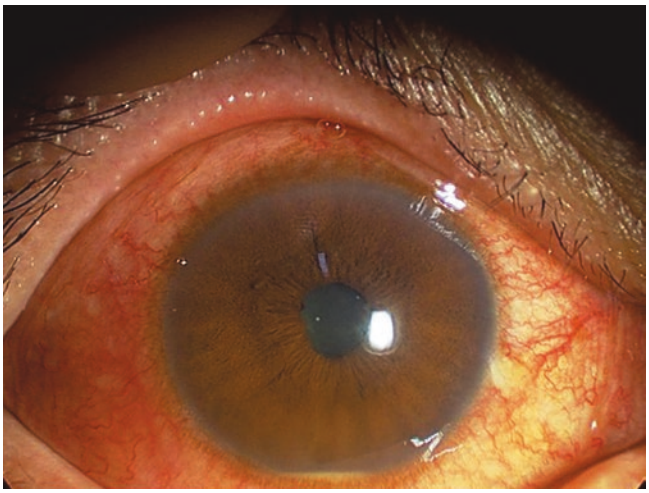

Fig. 31.1 Color photograph shows HLA-B27-associated anterior uveitis with bulbar conjunctival congestion, a small amount of hypopyon, and partial posterior synechia of iris

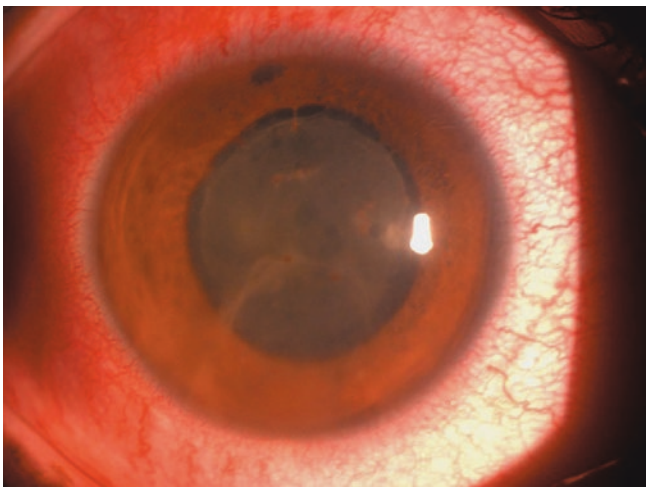

Fig. 31.2 Slit-lamp photograph shows HLA-B27-associated anterior uveitis with bulbar conjunctival congestion and fibrinoid exudation in anterior chamber

HLA-27 shall be paid attention to, and ESR, C-reactive protein, and imaging of sacroiliac joint. Especially for the patients with significantly elevated ESR and C-reactive protein, a consultancy of rheumatology department should be held to exclude diagnosis of related systemic disease, and topical corticosteroids and mydriatic drops would be applied for ocular treatment [3].

31.2.2 Uveitis Caused by Behcet's Disease

Uveitis caused by Behcet's disease is one of the most common panuveitis in China, which usually achieves poor prognosis. Ocular involvement occurred in approximately 34.8% of 1996 patients with Behcet's disease in a report of professor Zhang Zhuoli [4]. Professor Yang Peizeng reported that about 18% of patients with uveitis were suffering from Behcet's disease [5]. Ocular signs not only usually manifest as non-granulomatous uveitis, but also include some rare ocular manifestations such as punctate keratitis, annular corneal parenchyma opacity, and scleritis. Ocular inflammation is often bilateral but sometimes unilateral, and characterized by recurrence. Complications can frequently occur, such as complicated cataract and secondary glaucoma, optic and macular atrophy, and finally sharp, significant vision loss. Generally speaking, men are slightly more affected by uveitis than women, and can also have hypopyon. Therefore, the noninfectious uveitis manifested with a sign of hypopyon is usually seen in patients with Behcet's disease or HLA-B27-associated anterior uveitis.

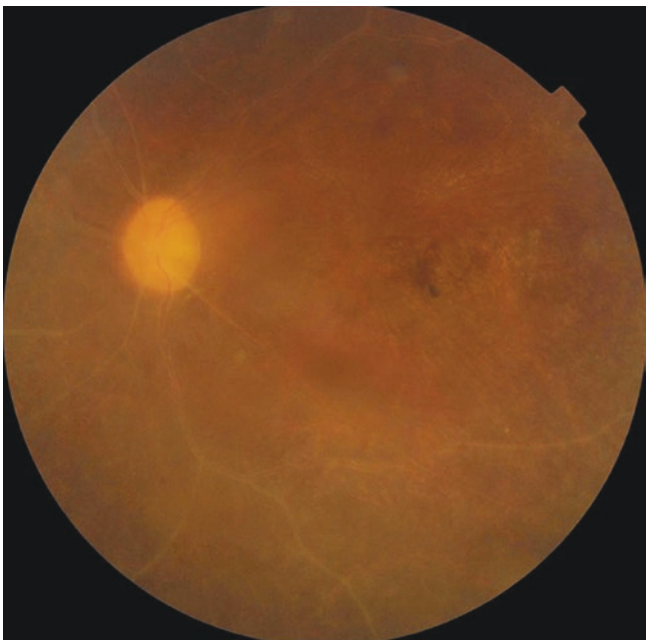

Fig. 31.3 Behcet's disease: color fundus photograph demonstrates optic atrophy and white-line-like blood vessels caused by retinal vascular occlusion

Retinal vasculitis is the most common manifestation occurring in posterior segment of Behcet's disease [6]. Fluorescein angiography demonstrates leakage of small vessels in retinitis which are the firstly involved by this disease, and might also show macrovascular leakage, staining of vascular wall, and macular edema. For the acute attack of uveitis with Behcet's disease, there can be multiple pieces of hemorrhages and exudation in the fundus, and in macular area for some patients, which could lead to significant vision loss. Patients with poor vision often combine with optic atrophy, and white-line-like blood vessels in retinal and macular atrophy (Fig. 31.3).

The diagnosis of Behcet's disease still follows the Criteria for Diagnosis of Behcet's Disease by the International Study Group for Behcet's Disease [7]. Corticosteroids and mydriatic drops for the eyes are applied for treatment of anterior

uveitis, as well as orally administrated corticosteroids combined with immunosuppressive agents systemically. For the critical patients, or the patients with repeated outbreak of inflammation, biological agents might also be applied as a combination for the treatment.

31.2.3 Systemic Lupus Erythematosus (SLE)

Both anterior and posterior segments can be involved in SLE, as keratitis, scleritis, and anterior uveitis presenting in anterior segment and hemorrhages, cotton wool spots, and retinal vessel occlusion manifesting in fundus (Fig. 31.4); there might also be papilledema or optic atrophy [8].

Laboratory tests for ANA, anti-dsDNA, and ESR are needed to exclude systemic diseases when these ocular performances are observed. Although ESR is a nonspecific indicator, it always demonstrates that systemic disease is combined when elevated. However, systemic disease cannot be ruled out just by normal ESR. Once any of the blood immunity indicators is found to be abnormal, patients should be highly recommended to ask doctor's advices of immunity department for systemic treatment. Patients with ocular involvement need topical therapy from ophthalmology department.

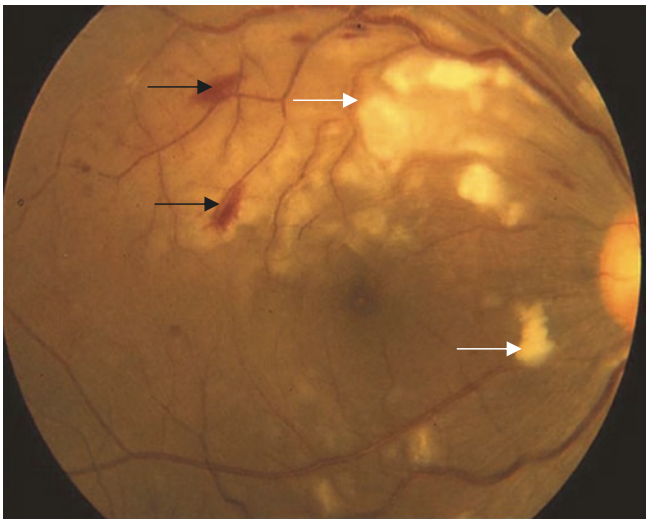

Fig. 31.4 Color fundus photograph of a patient with SLE. Note: Retinal hemorrhage (black arrow), cotton wool patches (white arrow), and superior temporal branch retinal artery occlusion

31.2.4 Scleritis

Scleritis is often seen in patients with autoimmunity diseases such as relapsing polychondritis, Wegener granulomatosis, rheumatoid arthritis, and systemic lupus erythematosus [9]. Figure 31.5 shows a case of bilateral temporal episcleritis which was supersymmetrical, and this patient presented with a red, painful eye. Ultrasound biomicroscopy (UBM) demonstrates episcleral tissue thickening and inflammatory changes (Fig. 31.6). The swelled external ear (Fig. 31.7)

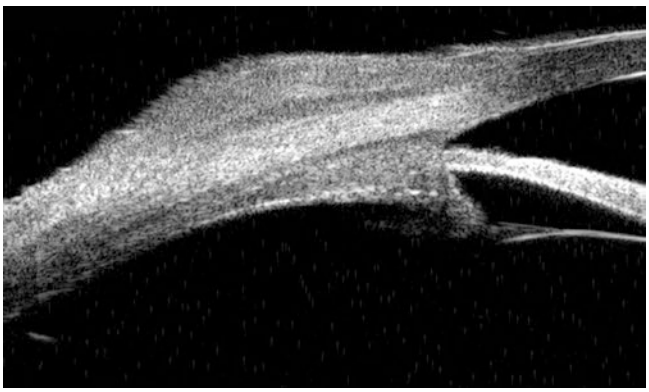

Fig. 31.6 Ultrasound biomicroscopy reveals episcleral tissue thickening and inflammatory changes

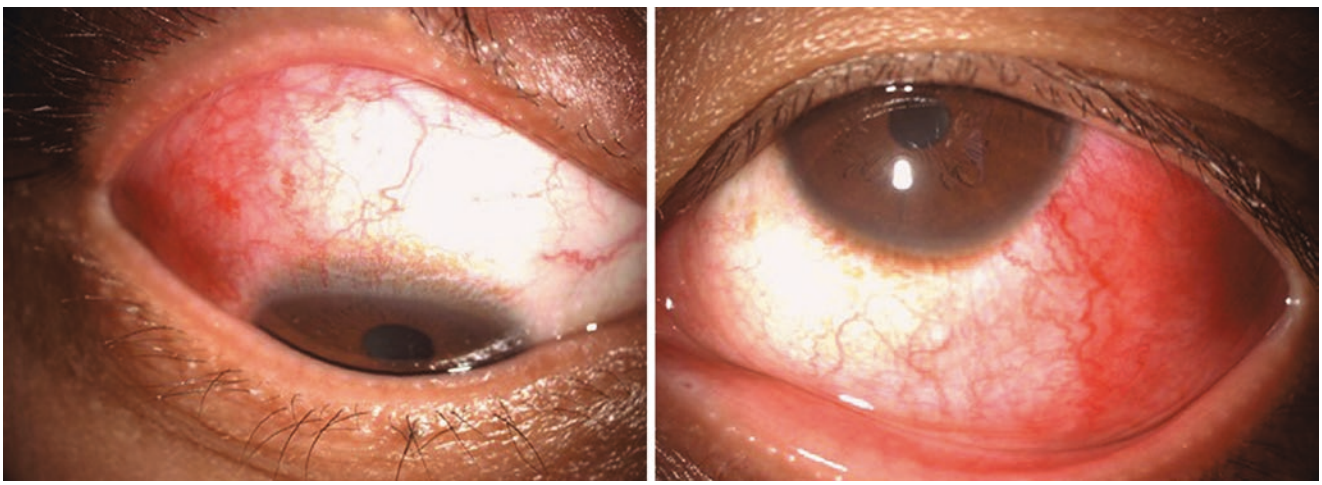

Fig. 31.5 Bilateral episcleritis

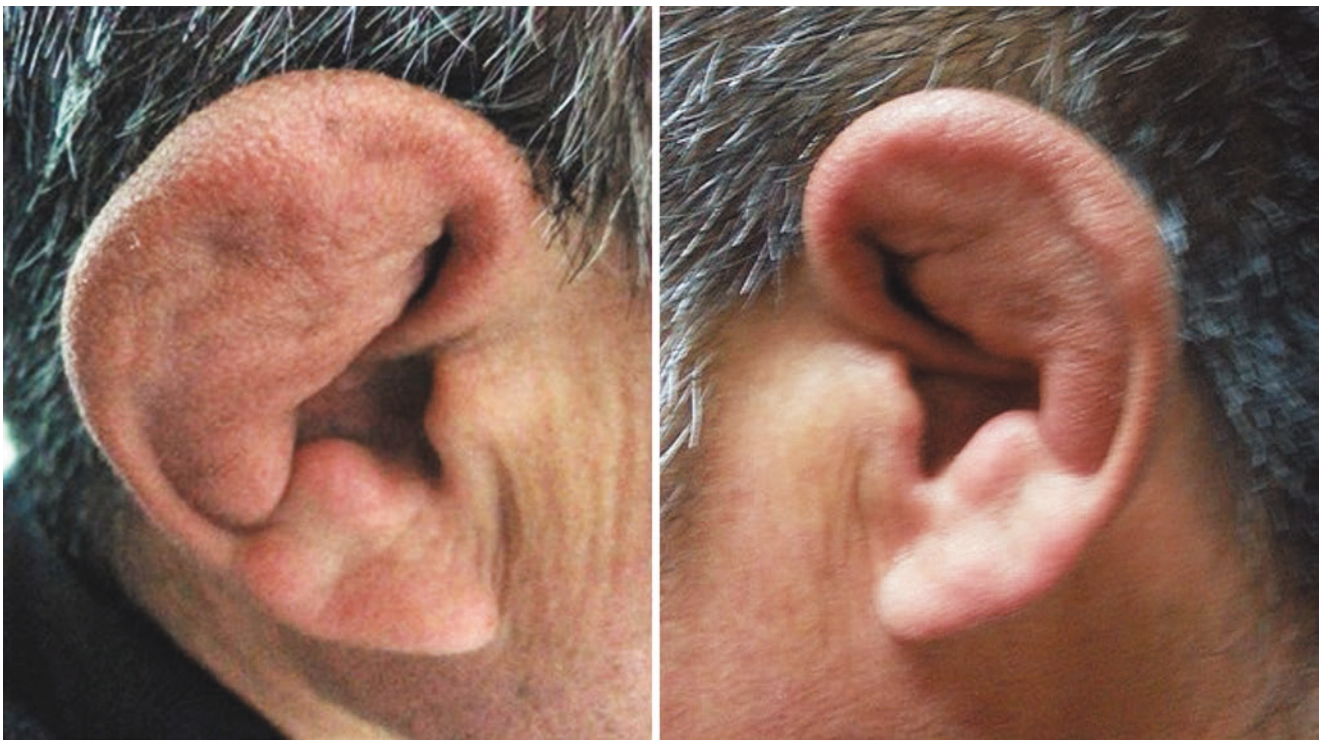

Fig. 31.7 This patient had elapsing polychondritis and swelled bilateral external ears

made us suggest him to see the doctor of immunity department, and finally relapsing polychondritis was diagnosed.

It's easy to diagnose scleritis according to the symptoms and signs. UBM for further examination helps to make a definite diagnosis and observe curative efficacy. Ocular B-scan ultrasonography can distinguish the form of scleritis—posterior or anterior. The blood immunity indices include rheumatoid factors, ESR, C-reactive protein, antinuclear antibodies, and antineutrophil cytoplasmic antibodies. Consultation of immunology department is necessary sometimes.

31.2.5 Juvenile Uveitis

Juvenile uveitis is not unusual among patients with uveitis, and some cases are accompanied by juvenile idiopathic arthritis [10]. Young girls are at high risk of it. The occurrence of this disease is relatively quiet, and the course of the disease is prolonged. It is often found by physical examinations in kindergarten or primary school that children were with poor vision, and prone to complications, such as band degeneration of corneal and complicated cataract. Anti-inflammatory treatment should be intensified, especially during the perioperative period. Cataract surgery is not recommended if good postoperative inflammatory control and follow-up are not achieved. To confirm the diagnosis of juvenile uveitis, patients should have joint swelling and pain, low-titer ANA positivity, and X-ray film of involved joints. Anterior uveitis is usually present, while a few patients have posterior segment involved such as optic edema, leakage of retinal vessels, and macular edema. Immunosuppressive treatment of methotrexate, cyclosporine, and even biological agents should be considered for active treatment on patients with recurrent inflammation and involved posterior segment, besides the topical anti-inflammatory therapy [11].

31.3 Differential Diagnosis of Uveitis

In some cases, general infectious disorders or tumors can be misdiagnosed as noninfectious uveitis for the manifestations in eyes, resulting in the misuse of corticosteroids and immunosuppressive agents. Thus, differential diagnosis of causes is essential to distinguish infectious uveitis or tumor before the treatment.

Infectious uveitis is mainly caused by viruses, bacteria, fungi, tuberculosis, and treponema pallidum. Intraocular tumors, such as juvenile retinoblastoma and adult intraocular lymphoma, can simulate intraocular inflammation, so-called masquerade syndromes. Figure 31.8 shows acute retinal necrosis (ARN) syndrome, caused by varicella zoster virus (VZV) or herpes simplex viruses (HSV), manifest as peripheral white or cream-colored retinal necrosis with retinal hemorrhages accompanied by retinal artery occlusion. Figure 31.9

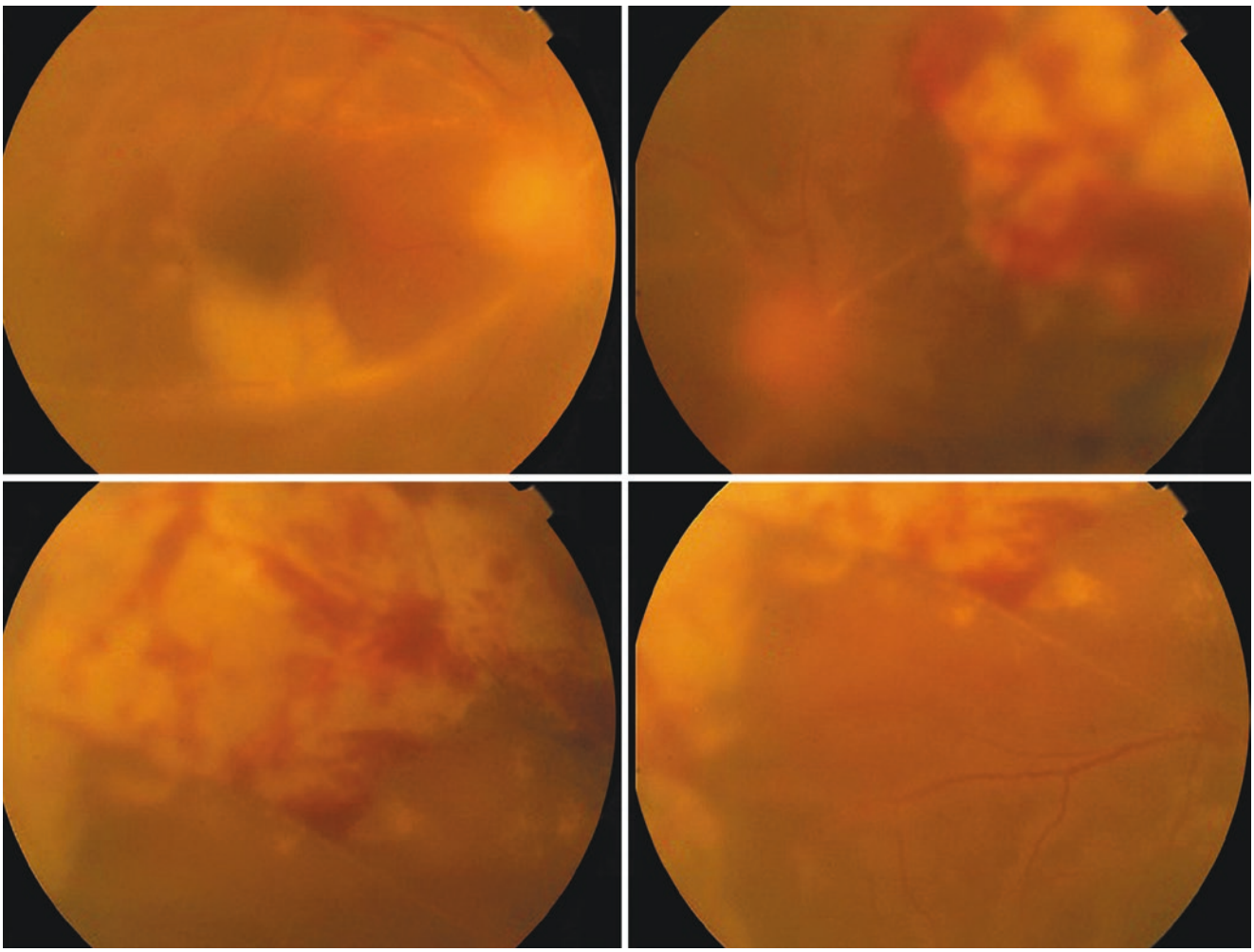

Fig. 31.8 Acute retinal necrosis: white-yellowish retinal necrosis and hemorrhages affecting the peripheral retina and retinal artery occlusion

presents the fundus of a patient with AIDS who was firstly diagnosed as cytomegalovirus retinitis. Figure 31.10 denotes the fungal endophthalmitis characterized by cotton-like opacity in vitreous body. Retinitis often relates to autoimmune or infectious disease, as indicated by Fig. 31.11, the binocular retinal vasculitis caused by tuberculosis. Figure 31.12 specifies the bilateral chorioretinitis due to syphilis.

There once was a patient, diagnosed with bilateral panuveitis, who had bilateral subacute progressive vision loss and retinopathy after treatments with corticosteroids, immunosuppressive agents, antiviral drugs, and antifungal agents. As indicated in Fig. 31.13, this patient was with optic disk edema and hemorrhage, numerous focal yellow-white granular areas in the periphery of the right eye; meanwhile, his left ocular fundus cannot be seen clearly as a result of the serious vitreous opacity which was finally confirmed as the diffuse large B-cell lymphoma (DLBCL) by vitreous biopsy. Figure 31.14 presents a middle-age male with bilateral central retinal vein occlusion showing increased ESR, diagnosed with multiple myeloma by hematology physician at last.

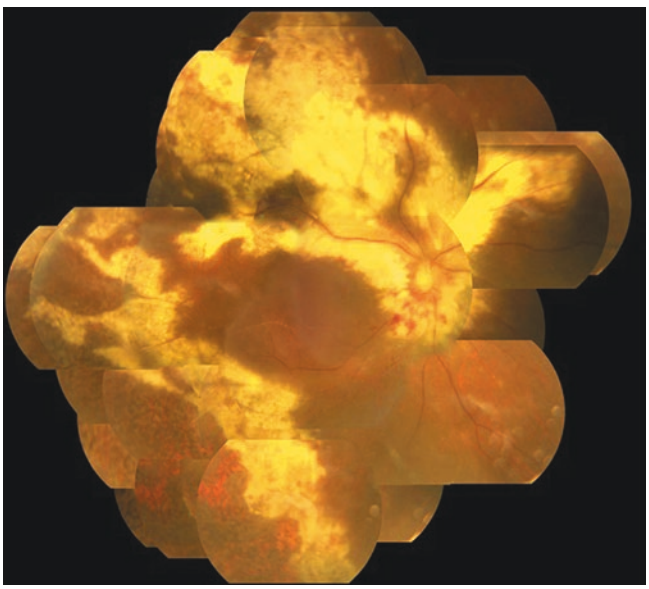

Fig. 31.9 Cytomegalovirus retinitis with the classic "tomato cheese-like" fundus in patient with AIDS

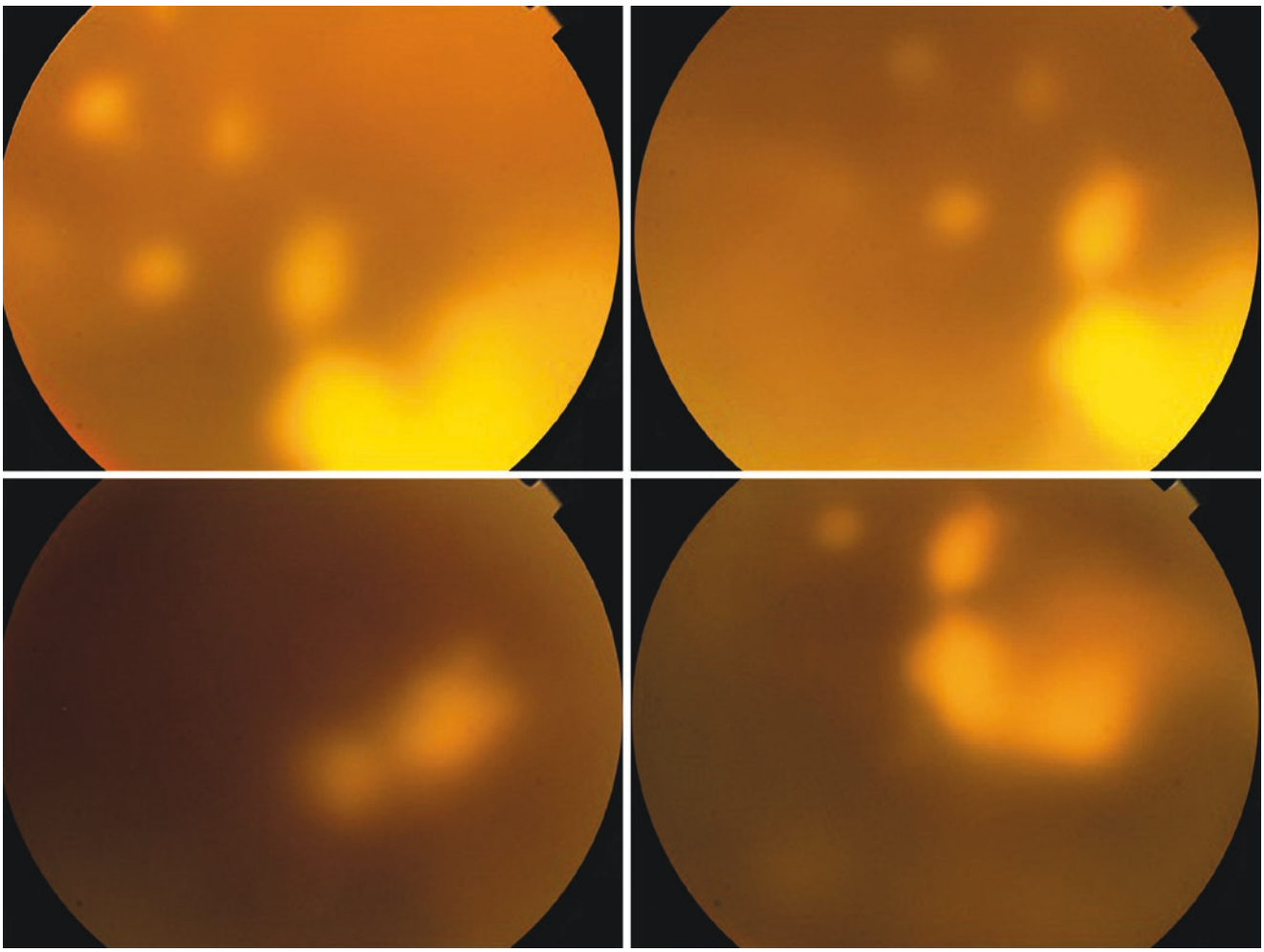

Fig. 31.10 Color photographs show multiple focal, round, white vitreous abscesses in a case of fungal endophthalmitis

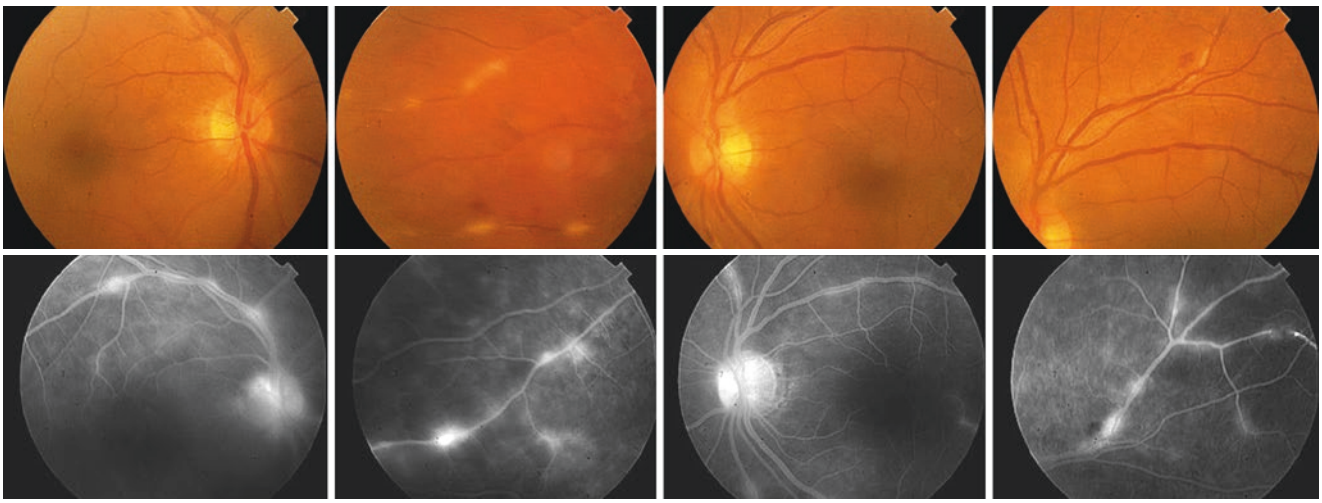

Fig. 31.11 Retinal vasculitis with inflammatory exudate from retinal vein and diffuse staining and leakage from the retinal vasculature in the late frames of the angiogram

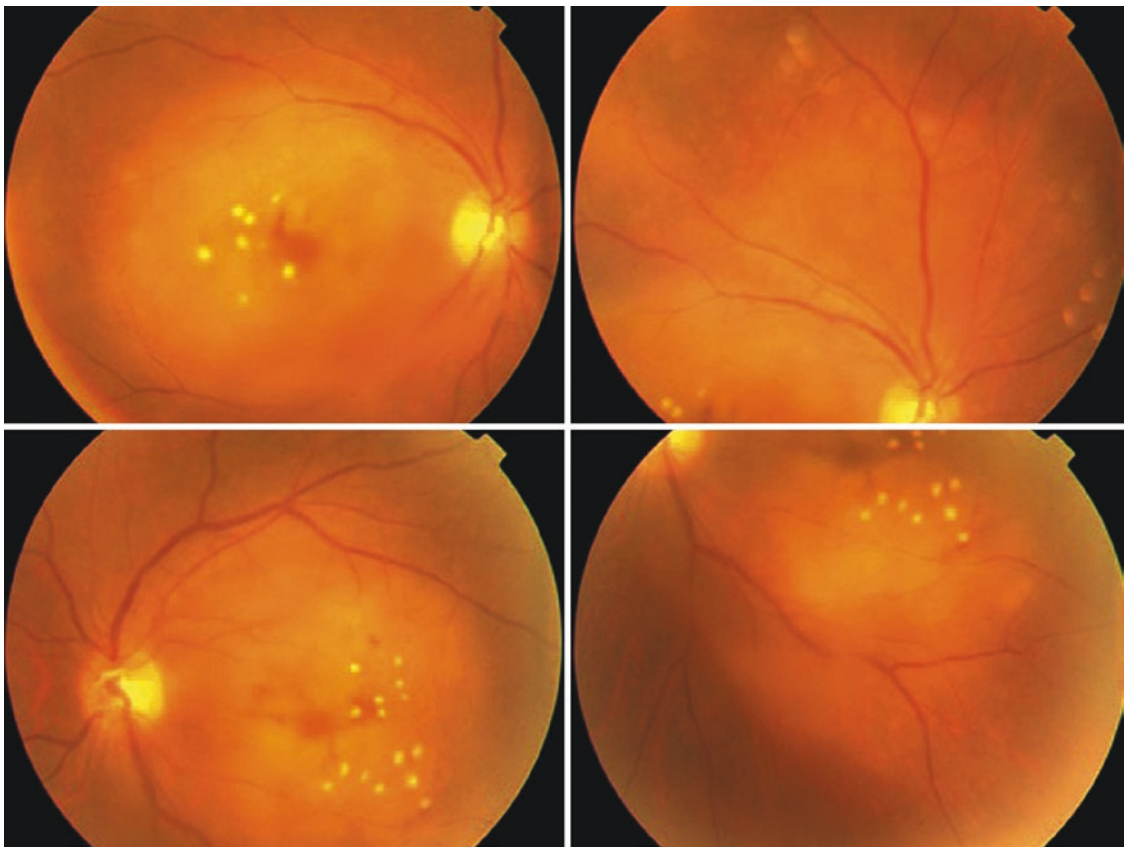

Fig. 31.12 The bilateral chorioretinitis caused by syphilis

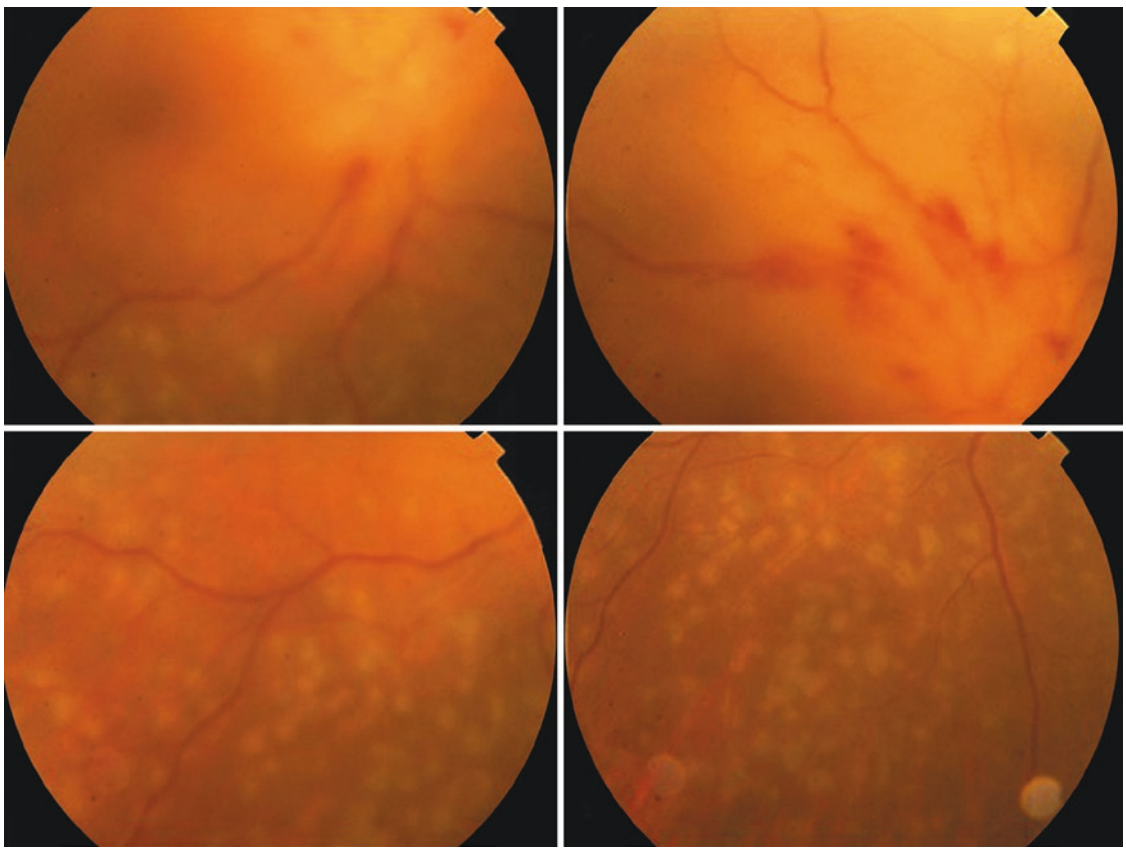

Fig. 31.13 There are multiple focal white-yellowish subretinal infiltrates involving inferior retina in a patient with primary intraocular lymphoma

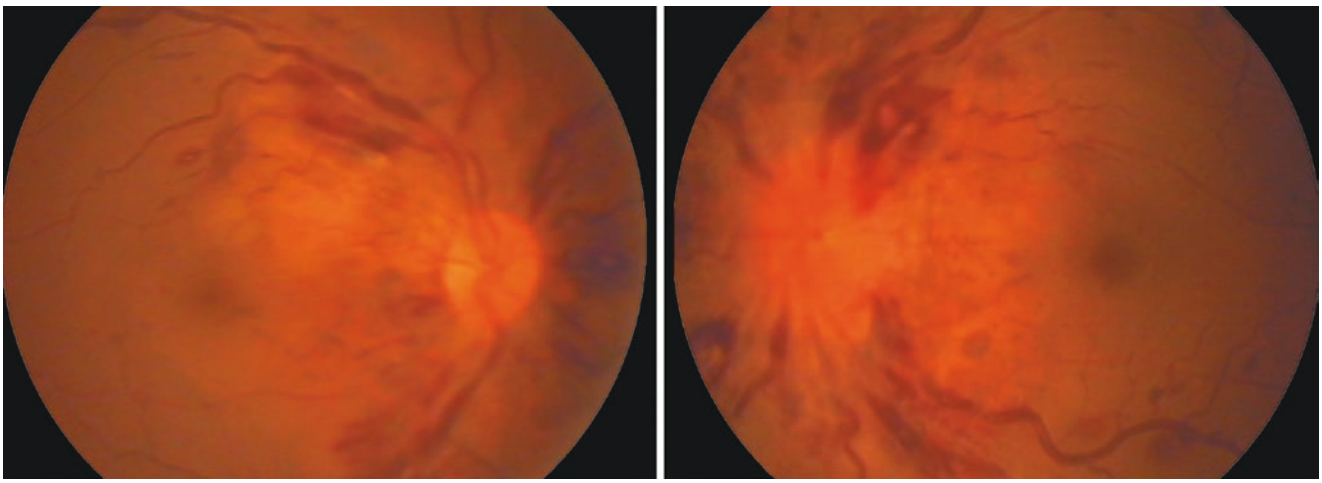

Fig. 31.14 This person had multiple myeloma masquerading as bilateral central retinal vein occlusion

Ocular involvements may occur in not only autoimmune disorders, but also infectious diseases and tumors; meanwhile, the signs are usually not specific. Thus, differential diagnosis is crucial to conduct correct general corticosteroid and immunosuppressive agent treatment. Once ocular involvements related to systemic disease are taken into consideration, cooperation of different departments is required for diagnosis and treatment.

References

1. Peizeng Y. Clinical uveitis. Beijing: People's Medical Publishing House; 2004.
2. Barisani-Asenbauer T, Maca SM, Mejdoubi L, et al. Uveitis—a rare disease often associated with systemic diseases and infections—a systematic review of 2619 patients. Orphanet J Rare Dis. 2012;7:57.
3. Wakefield D, Chang JH, Amjadi S, et al. What is new HLA-B27 acute anterior uveitis? Ocul Immunol Inflamm. 2011;19(2):139–44.
4. Zhuoli Z, Jinmin P, Xiaomeng H, et al. The meta-analysis of 1996 Chinese patients with Behcet's disease. Beijing Med J. 2007;29(1):10–2.
5. Peizeng Y, Zhen Z, Hong W, et al. Studies on the etiologies and classification of uveitis. Chin J Ocul Fund Dis. 2002;18(4):253–5.
6. Mendoza-Pinto C, Garcia-Carrasco M, Jimenez-Hernandez M, et al. Etiopathogenesis of Behcet's disease. Autoimmun Rev. 2010;9(4):241–5.
7. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990;335(8697):1078–80.
8. Davies JB, Rao PK. Ocular manifestations of systemic lupus erythematosus. Curr Opin Ophthalmol. 2008;19(6):512–8.
9. Mohsenin A, Huang JJ. Ocular manifestations of systemic inflammatory diseases. Conn Med. 2012;76(9):533–44.
10. Vitale AT, Graham E, de Boer JH. Juvenile idiopathic arthritis-associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome. Ocul Immunol Inflamm. 2013;21(6):478–85.
11. Pilly B, Heath G, Tschuor P, et al. Overview and recent developments in the medical management of paediatric uveitis. Expert Opin Pharmacother. 2013;14(13):1787–95.

Rheumatism and Rheumatic Ophthalmology from the Prospective of Integrative Medicine

32

Zhengang Wang and Ying Hong

32.1 Introduction

Rheumatic diseases are complex diseases involving systemic connective tissues. Although the manifestations of rheumatic diseases in joints, muscles, and other motor system have been well known, the ophthalmologists' awareness of rheumatic ocular disease is still inadequate. Rheumatic ophthalmopathy often becomes a disease difficult to diagnose that confuses clinicians, those who might neglect the screen of systemic diseases, thus leading to misdiagnosis and missed diagnosis. Therefore, the diagnosis and treatment of rheumatic ocular disease need to be combined with the concept of integrative medicine starting from the understanding of systemic diseases. The section introduces the relationship between rheumatism-caused systemic disease and ocular diseases; classification, clinical manifestations, and differential diagnosis of rheumatic ocular diseases; and treatment of systemic diseases. Thus ophthalmologists can understand and attach importance to ocular damage resulting from rheumatism, clear about the clinical manifestations of rheumatic diseases and rheumatic ocular diseases, clarify the etiology timely, and cooperate with rheumatologists, and thus then it would lead to treatment for the "disease," rather than "symptoms." At the same time, the section indicates the establishment of the concept for the interdisciplinary cooperative treatment of ophthalmology and rheumatic department for rheumatic ocular diseases, and discusses the possibility of developing specialized clinic for rheumatic ocular diseases, and standardized system for the diagnosis and treatment of rheumatic ocular diseases.

32.2 Rheumatic Diseases and Rheumatic Ocular Diseases from the Perspective of Integrative Medicine

Rheumatic diseases belong to a group of multisystem disorders with undetermined causes yet related to the immunodeficiency disorders. There are a variety of autoantibodies in the serum. The pathology is characterized by noninfectious, nonneoplastic inflammation, necrosis, granuloma, and vasculitis, which involves systems and organs of the whole body. Therefore, its clinical manifestations are complex and difficult to treat. The pain and functional disability of patients with rheumatism are the greatest harm of the disease. Some diseases can even cause the shortening of life.

As a part of our body, eye is rich in blood vessels and collagen tissue, which makes it frequently involved in rheumatic diseases. The so-called rheumatic ocular disease is the rheumatic disease associated with ocular involvement, and its clinical characteristics are similar to rheumatic disease itself. Functional disability (blindness) caused by its repeated attacks is the most serious consequences of rheumatic ocular disease. At some stages of the disease, some patients with rheumatic ocular disease only have local ocular manifestations, or have been accompanied with symptoms outside of eyes which indicates rheumatism. If the etiology of systemic disease screening was neglected, it would easily lead to misdiagnosis or missed diagnosis. Therefore, a look at the rheumatic ocular diseases from the perspective of integrative medicine is necessary, and rheumatologists and ophthalmologists should attach great importance to screening and treatment for rheumatic ocular diseases or immune-related ocular diseases.

32.3 Types and Categories of Rheumatic Ocular Diseases

Many ocular diseases are associated with rheumatic immune disorders, especially the ocular inflammatory disorders. In the case of uveitis, there are more than 30 categories of non-

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_32

Table 32.1 The relationship between systemic diseases and ocular diseases

	Uveitis	Superficial scleritis	Scleritis	Ulcerative keratitis	Retinal vasculitis	Orbital pseudotumor	Optic neuropathy	Ophthalmoplegia
Systemic lupus erythematosus	+++	++	++	++	++	+	++	+
Behcet's disease	++++							
Temporal arteritis	+	+	+++	+++	+	++	+	+
Takayasu arteritis				+	CRVO		++++	+++
Wegener's granulomatosis	+	++	+++	+		+		++
Takayasu arteritis					++		+	
Allergic granulomatosis				++	++	+		
Cogan syndrome				IK (interstitial keratitis)				
Relapsing polychondritis	++		++	++++	+			
Rheumatoid arthritis	++	+	+	+++				

inflammatory uveitis in *Clinical Uveitis*, edited by Peizeng [1]. In the *KELLEY'S Textbook of Rheumatology* (8th Edition), there are 16 types of ocular diseases associated with rheumatism [2] (Table 32.1). As further understanding for the mechanisms of some ocular diseases, new related diseases will be found.

Clinically, common rheumatic ocular diseases in rheumatology and ophthalmology are roughly divided into three categories:

The first category is for rheumatic ocular diseases, which take ocular involvement as one of the diagnostic criteria for rheumatic diseases. The relationship between this rheumatic ocular disease and rheumatic disease is very clear. Its presence or not is closely related to the diagnosis and treatment strategies for rheumatic disease. For example, recurrent acute iridocyclitis is one of the diagnostic criteria of spinal arthritis [3]; the same as uveitis of various types for Behcet's disease [4]; dry keratoconjunctivitis for primary Sjogren's syndrome [5]; various ocular inflammatory diseases for recurrent polychondritis [6]; the Gottron's rash on eyelid for dermatomyositis [7]; the presence of conjunctivitis for Reiter's syndrome and Kawasaki [8, 9]; non-syphilitic interstitial keratitis for typical Cogan syndrome [9], etc.

The second category is for rheumatic ocular diseases, which are often accompanied by or suggest the presence of rheumatism. This type of ocular diseases does not serve as a diagnosis criterion for rheumatic disease, yet still in some rheumatic diseases it occurs, or is featured, suggestive for the diagnosis [2]; for example, systemic lupus erythematosus (SLE)-related retinopathies (cotton-like exudation, etc.) are associated with systemic activity; systemic necrotizing vasculitides, such as granulomatous polyangiitis (GPA, formerly known as Wegener's granulomatosis), eosinophilic granulomatous polyangiitis (EGPA, formerly known as allergic granulomatous vasculitis), and microscopic polyangiitis (MPA) refer to various ocular inflammation with characteristic orbital involvement [10], as well as polyarteritis nodosa (PAN)-induced multi-site ocular involvement [9], corneal changes and uveitis of juvenile rheumatic arthritis (JRA) [9, 11], Steven-Johnson syndrome and ocular pemphigoid related ocular conjunctival involvement, multiple sclerosis (MS) [12]-induced optic neuritis and primary anti-phospholipid syndrome (APS)-associated retinopathies, etc. [9].

The third category is rare rheumatic diseases which are accompanied with ocular involvement, e.g., non-iridocyclitis ocular involvement in spinal arthritis (SpA) family (including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease arthritis), anterior ocular involvement in sarcoidosis, tuberculosis in rheumatic disease (Poncet syndrome), and so on; sclera involvement in rheumatic arthritis (RA); severe and irreversible ischemic retinal changes and others induced by giant cell arteritis (GCA) [13]; and in addition, many inflammatory ocular diseases with unknown causes, such as systemic sclerosis (SSc) and Takayasu arteritis (TA) [14].

Clinicians may have been familiar with the first type of rheumatic ocular diseases; nonetheless, for avoiding missed diagnoses, causes of the latter two types of rheumatic ocular diseases should also be paid attention to, especially the third category. Hence, only the concept of integrative medicine and thorough understanding of rheumatic diseases make it possible to rationally inspect the relationship between this kind of ocular diseases and systemic diseases.

32.4 The Common Points Between Rheumatic Disease and Rheumatic Ocular Disease

As one of the local manifestations of rheumatism, rheumatic ocular diseases belong to the category of immune-related inflammatory ocular diseases. Therefore, there are many similar characteristics between them: (1) the cause is unknown and the mechanisms are similar, both of which are related to the immune mechanism, and there are many

common inflammatory factors involved [15]; (2) serving as intersection of rheumatic disease and inflammatory ocular disease, the rheumatic ocular disease has two major clinical features: (a) it is with inflammatory ocular disease as the initial or primary symptom as attendance in the ophthalmology department and (b) a variety of rheumatic diseases can involve eyes [16, 17], and the various parts of the eye can be damaged by rheumatism. Therefore, the clinical manifestations of rheumatic ocular disease are very complex and extensive [14, 18]; (3) treatment strategies of the both diseases are similar, as sharing the principles as utilization of hormones and immunosuppressive agents in the severe and active period of the disease, timely control of inflammation, strictly preventing disease recurrence, and protecting visual acuity and function of involved organ; (4) the damages are similar; for example, the pain, blinding, labor disability, and causing of poverty and drug toxicity of rheumatic ocular diseases are similar to "5D" (disability, discomfort, death, drug-toxicity, dollar lost) in rheumatic diseases; (5) the problem to be studied is similar. Due to the impact of damage of rheumatic ocular disease on the patient's vision is more direct and more rapid, and since sudden blindness will cause severe trauma to patients' psychological and social role, rheumatologists and ophthalmologists should strive to save the vision of patients with rheumatic ocular diseases.

32.5 Renewal of Classification for Systemic Vasculitis and Single-Organ-Involved Ocular Vascular Diseases

Vasculitis refers to the disease manifested by the pathology of inflammation and destruction of blood vessels, while most of vasculitides are systemic diseases. A variety of causes can induce changes of vasculitis. Ocular vascular disease is the only visible vasculitis in vivo (such as fundus changes in patients with uveitis), belonging to the scope of small-vessel vasculitis. As early as in 2005, ophthalmologists have divided uveitis into two categories, primary and secondary vasculitis, each of which is divided into two subcategories as being limited to the ocular and associated with systemic diseases [19] (Table 32.2).

Clinicians often encounter vascular inflammatory lesions only limited to a certain organ, such as cutaneous vasculitis and pulmonary vasculitis. Vasculitis lesions only involving eye are not uncommon, e.g., Behcet's disease, Cogan syndrome, and granulomatous polyangiitis (formerly known as Wegener's granulomatosis), but Nomenclature of Systemic Vasculitides (CHCC1994) [20] based on the size of the affected blood vessels could not include all rheumatic diseases associated with vasculitis diseases. But the latest 2012 CHCC classification [21] criteria classify systemic vasculitis into seven categories, including vasculitis which is limited to an organ such as "isolated vasculitis" (Table 32.3).

Table 32.2 Classification of ocular inflammatory vasculopathies

Primary (ocular) inflammatory vasculopathy or vasculitis (the vessel is the primary target of the inflammatory process)	
1. Localized to the eye and adnexa	
2. Involving the eye and other organs (primary systemic vasculitides) (TA, PAN, Kawasaki, WG, CSS, anaphylactoid purpura, cutaneous leukocytoclastic vasculitis, cryoglobulinemic vasculitis, PMA)	
3. Orbital, periocular, and neuro-ophthalmological involvement—primary vasculitides (PAN, Kawasaki, WG, CSS, PMA)	
Secondary (ocular) inflammatory vasculopathies or vasculitides (vasculitis is the prominent feature but is secondary to an inflammatory process not primarily directed to the vessel)	
1. Localized to the eye or adnexa	(Immune, infection mediated, parasites, tumors)
2. Associated with systemic involvement	
Scleritis, keratitis (PUK)	(Immune, infection mediated)
Retinal vasculitis	(Immune, infection, virus mediated, parasites, drugs, tumors)
Choroidal inflammatory vasculopathy or vasculitis	(Immune, infection mediated)
Optic neuritis	(Immune, infection mediated)
Orbital, periocular, and neuro-ophthalmologic involvement	(Only immune-mediated ones are enumerated)

Table 32.3 Systemic vasculitis classification in 2012

Vasculitis classification	Common disease
Large-vessel vasculitis (LVV)	Takayasu arteritis (TAK); giant-cell arteritis (GCA)
Medium-vessel vasculitis (MVV)	Polyarteritis nodosa (PAN); Kawasaki disease (KD)
Small-vessel vasculitis (SVV)	Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) Microscopic polyangiitis (MPA) Granulomatosis with polyangiitis (Wegener's) (GPA) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Immune complex SVV Anti-glomerular basement membrane (anti-GBM) disease Cryoglobulinemic vasculitis (CV) IgA vasculitis (Henoch-Schönlein) (IgAV) Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
Variable-vessel vasculitis (VVV)	Behcet's disease (BD); Cogan syndrome (CS)
Single-organ vasculitis (SOV)	Cutaneous leukocytoclastic angiitis; cutaneous arteritis; primary central nervous system vasculitis and isolated aortitis
Vasculitis associated with systemic disease	Lupus vasculitis; rheumatoid vasculitis; sarcoid vasculitis
Vasculitis associated with probable etiology	Hepatitis C virus-associated cryoglobulinemic vasculitis; hepatitis B virus-associated vasculitis; syphilis-associated aortitis; drug-associated immune complex vasculitis; drug-associated ANCA-associated vasculitis; cancer-associated vasculitis

Combined with the new classification criteria for CHCC systemic vasculitides in 2012 and the classification points of ocular vasculitides, it can be seen that the similarity between the two categories is that the overall and local relationship of inflammatory ocular diseases is given the full attention.

32.6 The Differential Diagnosis of Rheumatic Ocular Disease

As same as rheumatic disease, the identification of rheumatic ocular disease also depends on careful differential diagnosis. Taking uveitis as an example, it is a kind of ocular autoimmune disease, and the relationship between it and the extraocular performance or systemic diseases is often neglected. Australian ophthalmologists [22] analyzed 2619 cases of uveitis (including 59.9% of anterior uveitis, 14.8% of intermediate uveitis, 18.3% of posterior uveitis, and 7.0% of all uveitis) and found that 37.2% of patients with uveitis had relationship with extraocular disease; joint performance accounted for 10.1%; noninfectious systemic diseases (e.g., BD, sarcoidosis, or multiple sclerosis) accounted for 8.4%; and infectious diseases accounted for 18.7% of the total number. 49.4% of patients with anterior uveitis were associated with HLA-B27 (+), the cause of posterior uveitis related to ocular toxoplasma (29%) and multifocal choroiditis (17.7%), which indicates that ophthalmologists, rheumatologists, doctors of infectious disease department, neurologists, and family doctors should be familiar with the differential diagnosis of uveitis and strengthen collaboration.

The differential diagnosis of rheumatic ocular disease needs to include at least eight aspects: (1) inflammatory diseases, which means primary autoimmune diseases. Clinically, although some rheumatic diseases have autoantibody-positive markers with characteristics of autoimmune diseases, the negative results of autoantibody detection could not make exclusion of diagnosis; (2) infectious and (3) infiltrative (referring in particular to invasive tumor diseases) diseases are the most important two types which need to be ruled out mostly in the differential diagnosis, and clinicians should give full consideration; (4) injurious diseases are the ones most commonly seen and most easily to be identified, while it should not be neglected on the history of vulnerable patients with a slight trauma; (5) iatrogenic ones need to be taken seriously and avoided, which is common in surgeries, trauma, or drug application; (6) inherited, such as metabolic or dystrophic diseases; (7) ischemic: ischemic ocular changes could be seen in any ocular blood circulation damage diseases, and is common in ischemia of eye and small-vessel disease ischemia such as retinal arteriovenous vascular disease caused by lesions in larger blood vessels such as carotid arteries or temporal arteries; (8) idiopathic ones, which are with causes unknown or cannot be identified by current means of inspection.

In the differential diagnosis of various inflammatory ophthalmopathies, it was found that the manifestations outside the eye, especially the involvement of adjacent organs of it, are critical for indicating the presence of systemic disease. Therefore, any evidence associated with rheumatic diseases is crucial for identifying the existence of the rheumatic ocular disease. Transfer biggest to key, due to the key difference between autoimmune response and autoinflammatory response is that whether there is detectable autoimmune antibodies or not, considering of the difference between basic medicine research and clinical applications, no clinically detectable autoimmune antibodies cannot completely have rheumatic immune disease excluded. Even there is no implication to systemic diseases; only with the basis of adequate differential diagnosis it would be reasonable to classify the confined ocular inflammatory diseases such as ocular vasculitis into rheumatic diseases [22].

32.7 Significance of Early Identification, Diagnosis, and Treatment of Rheumatic Ocular Diseases

The importance of identifying rheumatic ocular disease is that early treatment is an important part of preventing vision disability.

A set of data on the second national disability sample survey in 2006 [23] illustrates this point. Results of this survey showed that seven categories of disabled people accounted for 6.34% of the total population, including 14.86% of visual disability, among which there were cataract as 56.7%, uvea diseases as 14.1%, corneal diseases as 10.3%, ametropia as 7.2%, glaucoma 6.6%, and so on, many of which are classified into "causes unknown." It is reasonable to speculate that these unknown causes may be associated with rheumatic immune. This report had a gratifying message that the prevention and treatment of poliomyelitis had significantly reduced the incidence of physical disability sequelae (as 5.7% lower than the first census), which suggested that the results may be quite different if we focus on rheumatic ocular diseases and actively treat them.

Rheumatism is treatable and can be controlled. In recent years, the basic and clinical researches of rheumatism have made many progresses. Early diagnosis and early treatment, targeted treatment and standardized treatment, individualized treatment, and disease monitoring are the basic elements to treat and control rheumatic diseases; currently, rheumatic treatment goals have been transformed from symptom control to function maintain. A variety of new type of medicines had been applied for treating rheumatic diseases besides the most commonly used glucocorticoids and immunosuppressive agents, e.g., a variety of biological agents and small molecules newly developed, as well as multiple monitoring

methods and standards newly designed and improved for it. The 10-year change of RA situation correlates with the development of RA treatment concept and changes of drug trends [24]. And this fact can prove that changes in the treatment concept can significantly improve the prognosis of patients. The progress of the treatment concept for rheumatic might also brings new opportunities for the improvement of rheumatic disease treatment. It should be recognized that early screening and systemic treatment of rheumatic ocular disease means prevention of blindness and disability. From the perspective of the integrative medicine, the road of the basic and clinical researching of rheumatic ocular disease is right in front of us with broad outlook. In this area, ophthalmologists and rheumatologists need close cooperation.

32.8 Summary

Diagnosis and treatment of rheumatic ocular diseases are a new interdisciplinary attempt, and there is a lot unknown with high risk! Ophthalmologists and rheumatologists abroad have attempted to jointly treat rheumatic ocular diseases. The combination for it in the Ophthalmology and Rheumatology Department of Beijing Tongren Hospital had saved a large number of special patients successfully [14]. Practices have proved that the close cooperation of rheumatologists and ophthalmologists can cope with the new challenges of the diagnosis and treatment of rheumatic ocular diseases!

References

1. Peizeng Y. Classifications of uveitis. Beijing: People's Medical Publishing House; 2004.
2. Gabriel SE. KELLEY'S textbook of rheumatology (Chinese version). Translated by Li Zhanguo, Tang Fulin. Beijing: Peking University Medical Press; 2011.
3. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777–83.
4. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet. 1990;335:1078–980.
5. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61:554–8.
6. Michet CJ Jr, McKenna CH, Luthra HS, et al. Relapsing polychondritis. Survival and predictive role of early disease manifestations. Ann Intern Med. 1986;104:74–8.
7. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292:344–7.
8. Wu IB, Schwartz RA. Reiter's syndrome: the classic triad and more. J Am Acad Dermatol. 2008;59:113–21.
9. Mohsenin A, Huang JJ. Ocular manifestations of systemic inflammatory diseases. Conn Med. 2012;76:533–44.
10. Rothschild PR, Pagnoux C, Seror R, et al. Ophthalmologic manifestations of systemic necrotizing vasculitides at diagnosis: a retrospective study of 1286 patients and review of the literature. Semin Arthritis Rheum. 2013;42:507–14.
11. Edelsten C, Lee V, Bentley CR, et al. evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol. 2002;86:51–6.
12. Jasse L, Vukusic S, Durand-Dubief F, et al. Persistent visual impairment in multiple sclerosis: prevalence, mechanisms and resulting disability. Mult Scler. 2013;19:1618–26.
13. Liozon E, Ly KH, Robert PY. Ocular complications of giant cell arteritis. Rev Med Interne. 2013;34:421–30.
14. Zhengang W. Selected cases of eye & ENT involved in rheumatic diseases. Beijing: People's Medical Publishing House Co., Ltd.; 2012.
15. Horai R, Caspi RR. Cytokines in autoimmune uveitis. J Interf Cytokine Res. 2011;31:733–44.
16. McCluskey P, Powell RJ. The eye in systemic inflammatory diseases. Lancet. 2004;364:2125–33.
17. Menezo V, Lightman S. The eye in systemic vasculitis. Clin Med. 2004;4:250–4.
18. Shepherd JB 3rd. Ocular vasculitis. Curr Rheumatol Rep. 2003;5:100–6.
19. Herbort CP, Cimino L, Abu El Asrar AM, et al. Ocular vasculitis: a multidisciplinary approach. Curr Opin Rheumatol. 2005;17:25–33.
20. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: the proposal of an international consensus conference. Arthritis Rheum. 1994;37:187–92.
21. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus. Clin Exp Nephrol. 2013;17:603–6.
22. Barisani-Asenbauer T, Maca SM, Mejdoubi L, et al. Uveitis a rare disease often associated with systemic diseases and infections—a systematic review of 2619 patients. Orphanet J Rare Dis. 2012;7:57–64.
23. Bao T, Yang Z, Zhouying Q. Comparison and analysis of data obtained in two national sampling surveys of disability. Chin J Spec Educ. 2007;8:54–6.
24. Saeki Y, Matsui T, Saisho K, et al. Current treatments of rheumatoid arthritis: from the 'NinJa' registry. Expert Rev Clin Immunol. 2012;8:455–65.

Juvenile-Type Chronic Arthritis with Uveitis Cataract Surgery

33

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33.1 Introduction

Juvenile rheumatic arthritis is a common connective tissue disease occurring at age under 16. Its main feature is chronic arthritis, accompanied by involvement of multiple systems, and the ocular manifestation is mainly uveitis. Cataract is the most common complication of juvenile chronic arthritis associated with uveitis. Despite the high success rate of cataract surgery, compared with ordinary pediatric cataract surgery, cataract surgery in patients with juvenile chronic arthritis associated with uveitis has great particularity and complexity, as reflected by such issues as how to control systemic diseases, how to control inflammation of uveitis, how to manage the perioperative stage of cataract surgery, what are the chances and treatment of postoperative complications, and what is the difference in postoperative visual acuity improvement compared with normal cataract. They are all key issues to face in patients with juvenile chronic arthritis associated with uveitis and cataracts. This section describes the differential diagnosis of juvenile chronic arthritis associated with uveitis cataract, timing of surgery, perioperative inflammation control, choice of surgical methods, and other aspects. It suggests that the ophthalmologist should, on the basis of precise diagnosis, take into account the concomitant treatment of systemic diseases according to patient age, diagnosis, and inflammation severity, to improve the prognosis of cataract surgery for the patients with juvenile chronic arthritis associated with uveitis. It can help the ophthalmologist establish personalized cataract surgery treatment protocols that specifically address the key points of "rheumatic immune disease," "uveitis," and "juvenile."

The most common complication of juvenile chronic arthritis associated with uveitis is cataract, secondary to long-term intraocular inflammation or corticosteroid therapy, with an incidence of 40–60%. Although the cataract surgery for adults with uveitis has been well grasped and can generally produce good postoperative prognosis, cataract surgery related to children uveitis is still very challenging because of its particularity, and an efficacy standard that is generally accepted has not yet been established for it. Cataract surgery with phacoemulsification combined with primary lens implantation is considered safe and effective for children without uveitis over 2 years old, but its results are not equally applicable for the prediction of cataract surgery efficacy for children with uveitis. Among them, cataract surgery for juvenile chronic arthritis-associated uveitis often results in surgical failure because of a series of complications during and after the surgery (aftercataract, iris posterior synechiae, pupillary occlusion inducing glaucoma, low intraocular pressure, and even atrophy), which leads to worse visual prognosis. Even if the surgery succeeds, the prognosis of cataract surgery for patients with juvenile idiopathic arthritis (JIA) is often limited by optic nerve and macular degeneration and band-shaped corneal degeneration. Therefore, strengthened understanding of the disease, definite diagnosis, appropriate timing of surgery, perioperative inflammation control, surgical methods, reasonable choice of intraocular lens material, etc. are crucial for a successful cataract surgery for JIA patients.

33.2 Diagnosis

Uveitis accompanying JIA is mostly chronic recurrent anterior uveitis, occurring within 5 years after the occurrence of the JIA clinical manifestations. Its onset is insidious, and cataract is one of the major complications. Because of its occult onset, cataract is often the first symptom in the early stage of disease for children, so it is often misdiagnosed as "congenital cataract." It can be definitively diagnosed based on detailed history taking, typical clinical manifestations, arthropathy history, positive ANA results, etc. In our past

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https://doi.org/10.1007/978-981-13-7896-6_33

Table 33.1 Comparison between the diagnosis criteria from American College of Rheumatology and European League Against Rheumatism

	ACR[a]	EULAR[b]
Age onset	<16 years old	>16 years old
Arthritis	>6 weeks	>3 months
	Presence of joint swelling and articular exudation and at least two of the three symptoms below: Joint pain during joint motion or limited mobility, tenderness, local pyrexia	
Classification at 6 months after onset	Oligoarticular (<5 joints) Polyarticular (>4 joints) Systemic (articular, fever, rash)	Oligoarticular (<5 joints) Polyarticular (>4 joints) Systemic (articular, fever, rash) IgM-RF[c] negative
Others	Need to exclude juvenile ankylosing spondylitis, juvenile inflammatory bowel disease, juvenile psoriatic arthritis	Need to exclude juvenile ankylosing spondylitis, juvenile inflammatory bowel disease, juvenile psoriatic arthritis, and other juvenile arthritis

[a]*ACR* American College of Rheumatology
[b]*EULAR* European League Against Rheumatism
[c]*IgM-RF* IgM rheumatoid factor

research, 19 eyes of 10 cases with juvenile chronic arthritis (JCA) associated with uveitis complicated with cataract were observed. Among them, 7 patients (14 eyes) were diagnosed for JCA before the cataract surgery, and systemic administration of cyclophilin A orally, local cycloplegia, and glucocorticoid eye drops was done for 6 months to 1 year, and maintained for 6 months after surgery. Visual acuity improved to some extent for all patients. Three cases (five eyes) did not receive preoperative diagnosis for JCA and received the surgery for "congenital cataract." After a month, rapid onset of iritis was shown. The iritis is not easy to control by drug, resulting in pupillary occlusion, and three eyes had secondary glaucoma with a visual acuity that allows finger count only, and two eyes had eyeball atrophy with residual vision that allows only light perception. Thus, a definite diagnosis is essential to achieve a good prognosis before cataract surgery for patients with JIA-related uveitis. Treatment of JIA-associated uveitis complicated with cataracts as an ordinary cataract surgery will lead to severe and irreversible complications and seriously affect the postoperative visual acuity in children (Table 33.1).

33.3 The Timing of Surgery

Ophthalmic surgeons should ensure that the affected eye(s) of JIA patients has (have) been in the quiet stage of inflammation (less than one cell in anterior chamber or vitreous body) for at least 3 months before the cataract surgery. This has been shown to be able to reduce the incidence of postoperative CME [1]. In some cases, despite the use of large doses of immunosuppressive agents, intraocular inflammation has not been fully controlled, but urgent surgical treatment is needed, such as the intumescent cataract. In such cases, methylprednisolone 1 g intravenous treatment should be given 1 day before surgery [2]. If the disease is still active within 12 months after cataract surgery, the risk of complications will be greatly increased, and postoperative visual acuity will be greatly reduced [3]. Therefore, the surgery timing of JIA-related uveitis is very important. Clinical observation and massive search of literature support that uveitis has to be controlled for more than 3 months, preferably up to 6 months before cataract surgery [4].

33.4 Perioperative Inflammation Control

Among the (22 eyes of) 16 cases that received surgery for children cataract with uveitis reported by Celine Terrada, etc. [5], 9 cases suffered from juvenile arthritis. The mean preoperative oral prednisone is 29.5 mg/day. Oral steroid hormone increased in perioperative period (3 days) (prednisone 0.5 mg/kg/day) to glucocorticoid-dependent levels. Postoperative consolidation therapy is 8.13 mg/day on average. Five patients with JIA were treated with methotrexate at an average dose of 10–15 mg. All cases received preoperative local hormone therapy to keep the inflammation in the lowest level. In the first 4 days after the surgery, steroid hormone drops were applied every hour, and dexamethasone ointment was applied at night, after which the dose was reduced gradually according to the situation of inflammation. After an average follow-up of 6 years, CDVA of 19 eyes improved after surgery, 2 eyes stabilized at preoperative level, and 1 eye got worse after surgery. In the research of LINDA A et al. [6], six eyes of five cases with JIA received cataract phacoemulsification combined with intraocular lens implantation. Local glucocorticoid combined with systemic immunosuppressive agent administration was applied before the surgery. The median follow-up time was 43.5 months, after which the best corrected visual acuity in all patients was 20/40 or above. Probst and Holland [7] found that patients with JIA-associated uveitis treated with phacoemulsification and intraocular lens implantation had postoperative visual acuity of 20/40 or above after an average follow-up of 14 months. Lam et al. [6] reported that perioperative anti-inflammatory therapy contributed to prognosis in six eyes of five cases with JIA receiving intraocular lens implantation. Nemet et al. [8] have shown that the drug utilization for effective control of JIA and JIA-associated uveitis reduced postoperative complications [9]. Benezra and Cohen [10] thought that JIA-related uveitis children often suffered from postoperative complications because of postoperative aggravation of disease. Its control should be different from that for children with other types of uveitis after cataract surgery. Quinones et al. [11] pointed out that JIA patients could

achieve a better prognosis with immunosuppressive therapy. Therefore, a large number of articles in the literature and reports point out that the key success factor of cataract surgery for patients with juvenile chronic arthritis associated with uveitis is a positive preoperative and postoperative intraocular inflammation control, which is conducive to reducing intraoperative and postoperative complications. Systemic, local, and periocular steroid combined with systemic immunosuppressive therapy in the perioperative period is conducive to reducing cataract surgery complications in JIA-related uveitis patients [10] and realizing better postoperative visual acuity. Oral steroids should be given 3 days before the surgery, followed by reducing the use of steroids according to the postoperative inflammation gradually, and meanwhile add other immunosuppressive agents. In addition, if there is no ocular steroid injection contraindication, retrobulbar injection of steroid hormone (triamcinolone acetonide 40 mg/1 mL) may be performed. Local steroid and nonsteroidal anti-inflammatory drugs should be used perioperatively. In addition, some authors support injecting the antiseptic triamcinolone acetonide 4 mg/0.1 mL in the vitreous cavity at the end of the cataract surgery [12–14].

33.5 The Choice of Surgical Methods

Previously, because of severe inflammation after the cataract surgery in children and fibrin response in all cases, ocular implantation of intraocular lens for JIA and chronic uveitis patients is considered a contraindication. The reports [15, 16] of 1990s did not support intraocular lens implantation for cataract surgery secondary to uveitis in children. The reports pointed out that the safe and effective surgical procedures were vitrectomy, lens aspiration, and no intraocular lens implantation. Children with uveitis patients are sometimes not suitable for wearing contact lenses because of band-shape corneal degeneration, resulting in high risk of irreversible amblyopia for children. However, with the emergence of modern intraocular lens, as long as the inflammation is well controlled, intraocular lens implantation is also considered safe and reliable in these difficult cases. It is found that intraocular lens implantation after cataract phacoemulsification can achieve good vision prognosis [7]. Probst and Holland [7] followed the patients for an average of 14 months, after which they found that the postoperative visual acuity after intraocular lens implantation for cataract treatment for JIA-related uveitis patients was 20/40, or even better. Some studies recommend that intraocular lens implantation be performed during cataract surgery for JIA patients with effective perioperative inflammation control and close postoperative follow-up. However, for chronic, poorly controlled uveitis patients, intraocular lens implantation should be postponed [17–23]. Alio and others [24, 25] found that monolithic acrylic lens had the best biocompatibility for the anterior chamber and the lens capsule among the options of intraocular lens. Silicone lens had the highest incidences of posterior capsule opacity and cystoid macular edema. Hydrophilic acrylic lenses have a higher biocompatibility with the uvea than the hydrophobic body, while the hydrophobic acrylic lens has a higher biocompatibility for lens capsule. Thorough removal of viscoelastic agent behind the intraocular lens at the end of operation can reduce the space behind the intraocular lens, which helps to reduce the formation of aftercataract due to epithelial cell migration. Stressing to make hydrophobic acrylic IOL cling on to the posterior capsule can reduce the incidence of aftercataract [26]. In the choice of intraocular lens, it is confirmed by comparison that the long-term safety of modern hydrophilic acrylic acid IOL is better with better uvea biocompatibility and less posterior capsule complications, which results in better visual acuity [27, 28].

33.6 Summary

Surgery for complicated cataract in JIA-related uveitis is still challenging, and the ocular morbidity continues into adulthood. Complicated cataracts in JCA need to be regarded with caution. Preoperative and postoperative glucocorticoid and other immunosuppressive agents' rational application and close follow-up to ensure the treatment efficacy are very important. Patients' age, diagnosis, inflammation, and preoperative visual acuity should be fully taken into account before the surgery to develop a personalized treatment program for patients, which is critical for the prognosis. Appropriate follow-up time and content after the surgery should be developed, and CDVA, intraocular pressure, intraocular inflammation, and local or systemic drug treatment should be evaluated at follow-up visits, which plays a "preemptive management" role against postoperative complications.

References

1. Rojas B, Zafirakis P, Foster CS. Cataract surgery in patients with uveitis. Curr Opin Ophthalmol. 1997;8(1):6–12.
2. Belair ML, Kim SJ, Thorne JE, et al. Incidence of cystoid macular edema after cataract surgery in patients with and without uveitis using optical coherence tomography. Am J Ophthalmol. 2009;148(1):128–35.
3. Matsuo T, Takahashi M, Inoue Y, et al. Ocular attacks after phacoemulsification and intraocular lens implantation in patients with Behcet disease. Ophthalmologica. 2001;215(3):179–82.
4. Adan A, Gris O, Pelegrin L, et al. Explantation of intraocular lenses in children with juvenile idiopathic arthritis-associated uveitis. J Cataract Refract Surg. 2009;35(3):603–5.
5. Terrada C, Julian K, Cassoux N, et al. Cataract surgery with primary intraocular lens implantation in children with uveitis: long-term outcomes. J Cataract Refract Surg. 2011;37(11):1977–83.

6. Lam LA, Lowder CY, Baerveldt G, et al. Surgical management of cataracts in children with juvenile rheumatoid arthritis-associated uveitis. Am J Ophthalmol. 2003;135(6):772–8.
7. Probst LE, Holland EJ. Intraocular lens implantation in patients with juvenile rheumatoid arthritis. Am J Ophthalmol. 1996;122(2):161–70.
8. Nemet AY, Raz J, Sachs D, et al. Primary intraocular lens implantation in pediatric uveitis: a comparison of 2 populations. Arch Ophthalmol. 2007;125(3):354–60.
9. Oren B, Sehgal A, Simon JW, et al. The prevalence of uveitis in juvenile rheumatoid arthritis. J AAPOS. 2001;5(1):2–4.
10. Benezra D, Cohen E. Cataract surgery in children with chronic uveitis. Ophthalmology. 2000;107(7):1255–60.
11. Quinones K, Cervantes-Castaneda RA, Hynes AY, et al. Outcomes of cataract surgery in children with chronic uveitis. J Cataract Refract Surg. 2009;35(4):725–31.
12. Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. Ophthalmic Res. 2006;38(4):218–45.
13. Okhravi N, Morris A, Kok HS, et al. Intraoperative use of intravitreal triamcinolone in uveitic eyes having cataract surgery: pilot study. J Cataract Refract Surg. 2007;33(7):1278–83.
14. Dada T, Dhawan M, Garg S, et al. Safety and efficacy of intraoperative intravitreal injection of triamcinolone acetonide injection after phacoemulsification in cases of uveitic cataract. J Cataract Refract Surg. 2007;33(9):1613–8.
15. Foster CS, Barrett F. Cataract development and cataract surgery in patients with juvenile rheumatoid arthritis-associated iridocyclitis. Ophthalmology. 1993;100(6):809–17.
16. Kanski JJ. Juvenile arthritis and uveitis. Surv Ophthalmol. 1990;34(4):253–67.
17. Hooper PL, Rao NA, Smith RE. Cataract extraction in uveitis patients. Surv Ophthalmol. 1990;35(2):120–44.
18. Foster CS, Fong LP, Singh G. Cataract surgery and intraocular lens implantation in patients with uveitis. Ophthalmology. 1989;96(3):281–8.
19. Flynn HW Jr, Davis JL, Culbertson MW. Pars plana lensectomy and vitrectomy for complicated cataracts in juvenile rheumatoid arthritis. Ophthalmology. 1988;95(8):1114–9.
20. Kanski JJ, Shun Shin GA. Systemic uveitis syndromes in childhood: an analysis of 340 cases. Ophthalmology. 1984;91(10):1247–52.
21. Holland GN. Intraocular lens implantation in patients with juvenile rheumatoid arthritis-associated uveitis: an unresolved management issue. Am J Ophthalmol. 1996;122(2):255–7.
22. Fox GM, Flynn HW Jr, Davis JL, et al. Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis. Am J Ophthalmol. 1992;114(6):708–14.
23. Wolf MD, Lichter RR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology. 1987;94(10):1242–8.
24. Tessler HH, Farber MD. Intraocular lens implantation versus no intraocular lens implantation in patients with chronic iridocyclitis and pars planitis: a randomized prospective study. Ophthalmology. 1993;100(8):1206–9.
25. Alio JL, Chipont E, Benezra D, et al. Comparative performance of intraocular lenses in eyes with cataract and uveitis. J Cataract Refract Surg. 2002;28(12):2096–108.
26. Tomlins PJ, Sivaraj RR, Rauz S, et al. Long-term biocompatibility and visual outcomes of a hydrophilic acrylic intraocular lens in patients with uveitis. J Cataract Refract Surg. 2014;40(4):618–25.
27. Abela-Formanek C, Amon M, Kahraman G, et al. Biocompatibility of hydrophilic acrylic, hydrophobic acrylic, and silicone intraocular lenses in eyes with uveitis having cataract surgery: long-term follow-up. J Cataract Refract Surg. 2011;37(1):104–12.
28. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol. 2003;87(7):879–84.

34 Endogenous Endophthalmitis from the Prospective of Integration Medicine

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34.1 Introduction

Endophthalmitis is the acute suppurative inflammation in uvea and retina, with rapid onset, severe symptoms, and poor prognosis. Definite diagnosis and effective treatment on early stage play key roles in the prognosis. As endogenous endophthalmitis originates from suppurative inflammation in other parts of our body with hidden primary lesions, and is found less common in clinical practice, ophthalmologists might easily confuse it with uveitis caused by the immune disease, which not only causes a high misdiagnosis rate, but also delays the best opportunity for diagnosis and treatment. Endogenous endophthalmitis is a focus secondary to systemic infection, requiring ophthalmologists to strengthen the understanding of systemic infection and detailed history taking, to learn that whether the primary lesions exist or not? Where is the primary lesion? Which kind of pathogen causes the infection? How to apply the antibiotics? This section analyzes the cases of endogenous endophthalmitis in Tongren Hospital, and summarizes the experience in etiology, clinical manifestation, diagnosis points, treatment, prognosis, etc. of endogenous endophthalmitis. Ophthalmologists are supposed to take endogenous endophthalmitis from the perspective of integrative medicine, identify endogenous endophthalmitis through the history and pathogen examination, and clarify the cause and pathogens, and thus target the selection of antibiotics, taking the systemic inflammation control into account. Ophthalmologists should strengthen the understanding of endogenous endophthalmitis, make diagnosis at early stage and apply the effective drug timely, and improve the prognosis of endogenous endophthalmitis.

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Endogenous endophthalmitis refers to the uvea, retina, vitreous, and other intraocular tissue inflammation caused by bacteria or fungi infiltrating into eyeball through the blood circulation. The incidence of endogenous endophthalmitis accounts for 2–15% of the incidence of endophthalmitis, which has onset hidden while progresses rapidly, and frequently causes ocular atrophy and permanent loss of vision.

34.2 Endogenous Endophthalmitis from the Perspective of Integrative Medicine

Bacteria or fungi infiltrate the blood and cause bacteremia; that is, when patients are immunocompromised, the pathogens would easily enter the vitreous body and aqueous humor, promptly causing endophthalmitis. Some risk factors have been found to be associated with the occurrence of endogenous endophthalmitis. The patients are often accompanied by inducible diseases such as diabetes, heart disease, malignant tumor, cirrhosis, and acquired immunodeficiency syndrome; or with infected lesions such as liver abscess, meningitis, endocarditis, genitourinary infection, respiratory infection, and gastrointestinal bacterial infection; or other factors that cause the reduced immune system, like immunosuppressant use (glucocorticoid use, malignant tumor chemotherapy), intravenous drug abuse, recent surgery, trauma, and age. Patients with susceptibility factors accounted for 78.1–90% of patients with endogenous endophthalmitis [1]. Among them, the most common reason was diabetes, accounting for 33–62% [2–5]; and the infectious disease was liver abscess [5].

Data of 24 patients (32 eyes) who were clinically diagnosed as endogenous endophthalmitis in Beijing Tongren Hospital from January 2009 to January 2013 was analyzed, and 19 patients (79.2%) had a clear history of systemic disease, among whom 10 cases (41.7%) had systemic internal medical diseases or factors causing compromised immune system, including 4 cases (16.7%) with diabetes, 3 cases (12.7%) of postoperation (induction labor, gallstones, kidney

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_34

stones), 2 cases (8.3%) of continuous high-intensity work, and 1 case (4.2%) with long-term use of immunosuppressive agents. Nine cases (37.5%) had clear infection, including two cases (8.4%) with liver abscess, two cases (8.4%) of urinary tract infection, two cases (8.4%) of vaginal inflammation, one case (4.2%) of oral infection, one case (4.2%) with bacterial meningitis, and one case (4.2%) with respiratory infection. Sixteen patients (66.7%) had fever before the presence of ocular symptoms or accompanied the ocular symptoms. Fever is a manifestation of bacteremia caused by systemic immunity compromise. Therefore, endogenous endophthalmitis is supposed to be considered from the perspective of the integrative medicine. Patients often have diseases or incentives leading to a compromised immune system. If neglecting the medical history taking for systemic diseases, it would be easy to misdiagnose or miss diagnoses.

34.3 Common Pathogens of Endogenous Endophthalmitis

Endogenous endophthalmitis is divided into fungal endogenous endophthalmitis and endogenous bacterial endophthalmitis.

50% of endogenous endophthalmitis is caused by fungal infections [6], of which *Candida* is the most common, accounting for 33–80% [4, 7–9], followed by *Aspergillus*, accounting for 11.1–18.9% [9–11]. Other common fungal species include *Blastomycetes*, *Cryptococcus neoformans*, *Coccidioides*, Branches, and other species.

Fungal endophthalmitis is rarely seen before 1970s. In recent years, due to wide application of broad-spectrum antibiotics, immunosuppressive agents, glucocorticoids, cytotoxic drugs, as well as more and more diabetes, malignant tumor, AIDS, and other diseases causing compromised immune system, fungal infection increases significantly, of which the highest proportion is *Candida*, about 53.2% [12–14]. *Candida* is a symbiotic flora of the human body, which can store itself in the surface of human body, mouth, vaginal mucosa, and other parts, and serve as a conditional pathogen, which can cause systemic infection when the immune system of our body is compromised.

A variety of bacteria can cause endogenous endophthalmitis, e.g., *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Proteus bacillus*, *Pseudomonas*, and *Escherichia*. In Western countries, Gram-positive bacteria are the main pathogen, especially *Streptococcus* [15], and in the Asian population, Gram-negative bacteria are more common, especially *Klebsiella pneumonia* [16].

24 cases (32 eyes) of endogenous endophthalmitis from Beijing Tongren Hospital in recent years were analyzed. We performed vitrectomy for 31 eyes and conducted pathogen cultivation for vitreous body from the operation. Results showed that 17 eyes (54.8%) were positive, of which 14 eyes (45.2%) were fungi, including 7 eyes (22.6%) of *Candida albicans*, 3 eyes (9.7%) of *Candida*, 2 eyes (6.5%) of *Candida ciferrii*, 1 eye (3.2%) of *Candida guilliermondii*, and 1 eye (3.2%) of *Candida tropicalis*; 3 eyes (9.7%) were with bacteria, including 2 eyes (6.5%) of *Klebsiella pneumoniae* and 1 eye (3.2%) of *Aerococcus viridans*. Only 5 eyes of the total 31 eyes (6.1%) were positive for aqueous humor smear and 4 eyes (12.9%) were with hyphae visible. One eye (3.3%) was positive for *Klebsiella pneumonia* in the results of aqueous humor culture, and G+ bacteria was seen by aqueous humor smear.

34.4 Clinical Manifestations of Endogenous Endophthalmitis

There is no difference in the incidence of endogenous endophthalmitis among population of different sex or age. It was studied and suggested that, since the right eye is closer to the right arteria carotis communis, accepting more blood supply, the right eye had higher morbidity for endophthalmitis [3]. 24 cases of endogenous endophthalmitis from Beijing Tongren Hospital were with the gender ratio as 1:1, and the age range of onset was from 13 to 73 years with the average age as (42.46 ± 13.65) years. The incidence ratio of left to right was 1:1.46.

Characterized by the clinical manifestations, there are four categories of endogenous bacterial endophthalmitis: anterior and posterior focal infection, and anterior and posterior diffuse infection [17]. This classification originates from the onset site of the disease as the anterior infection firstly occurs in the pars plana of ciliary body, and the posterior bacterial endophthalmitis starts from the optic nerve choroid. Due to the rapid development of endogenous bacterial endophthalmitis in general, diffuse endophthalmitis can be revealed quickly, manifesting persistent high intraocular pressure, conjunctival edema, corneal edema, large fibrin exudation in anterior chamber, lens opacity, organization of hypopyon in vitreous body, and yellow-white reflect light in pupil area (Fig. 34.1) [18].

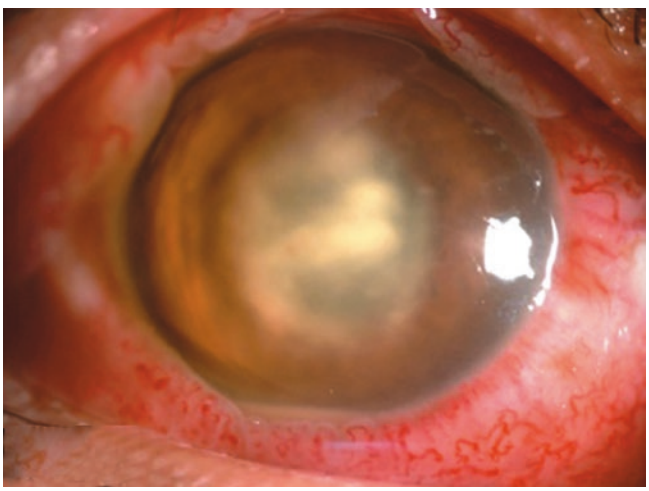

Fig. 34.1 Endogenous bacterial ophthalmitis

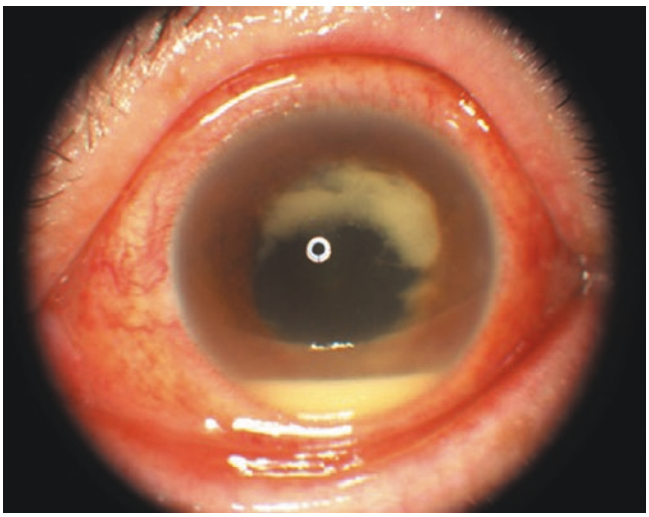

Fig. 34.2 Endogenous fungal ophthalmitis

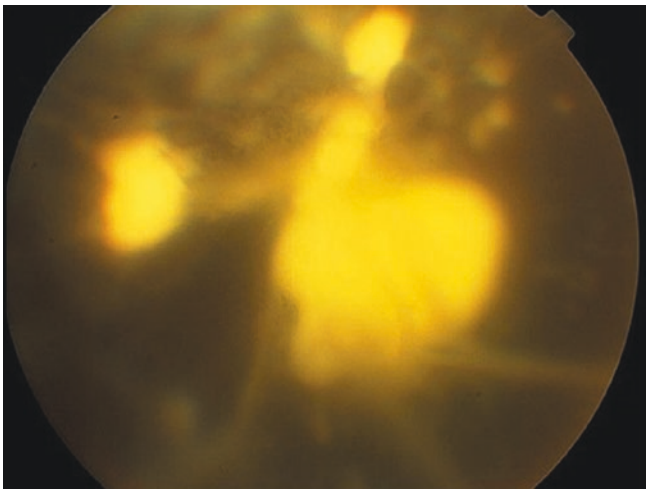

Fig. 34.3 Endogenous fungal ophthalmitis

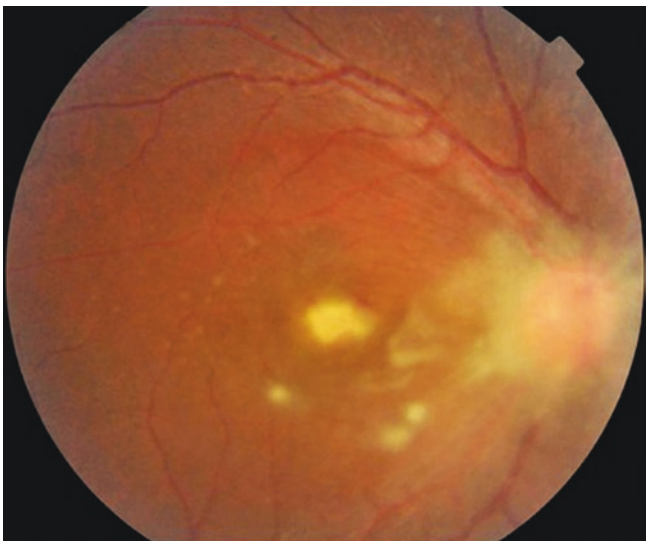

Fig. 34.4 Endogenous fungal ophthalmitis

The typical clinical manifestations of endogenous fungal endophthalmitis are toothpaste-like hypopyon (Fig. 34.2); pompon-like or jellylike vitreous opacity (Fig. 34.3); and retinal or subretinal yellow-white lesions with clear border (Fig. 34.4) [19]. The endogenous fungal endophthalmitis can be divided into four stages [20]: stage I: chorioretinal change without involving the vitreous cavity; stage II: the growth of fungus passing through the inner limiting membrane in the vitreous cavity; stage III: vitreous cavity opacity leading to the fundus invisible; stage IV: retinal detachment combined with stage III change. Due to fungal pathogenic characteristics, its development is not as rapid as bacteria.

34.5 Diagnosis of Endogenous Endophthalmitis

The diagnosis of endogenous endophthalmitis is mainly based on the risk factors for the patients, typical clinical manifestations, laboratory tests, and auxiliary examinations.

Intraocular fluid microbiological examination is the most valuable and reliable diagnostic method for endophthalmitis. Obtaining intraocular fluid, through anterior chamber penetration, vitreous aspiration, or vitrectomy for smear, culture, or PCR detection, is of great significance to the disease diagnosis and medical treatment. Positive results are easy to obtain by vitreous smear and culture; meanwhile, the positive rate of aqueous humor culture is not high.

24 cases (32 eyes) of endogenous endophthalmitis from Beijing Tongren Hospital analyzed in recent years had 11 from 31 eyes (35.5%) with positive results of vitreous smear, 17 eyes (57.9%) with positive results after vitreous culture, 5 cases (16.1%) with positive results of aqueous humor smear, and 1 case (3.2%) with positive results after aqueous humor culture. For the patients to whom the antibacterial treatment is effective without positive results for aqueous humor or vitreous body culture, the possible reasons could be as follows: (1) application of antibiotics or antifungal drugs before sampling and (2) relatively small sample size.

The misdiagnosis rate of endogenous endophthalmitis is above normal, especially in the early stages of the disease. The misdiagnosis rate of the disease could be up to 16–63% [1, 21–22]. Due to lack of specificity of early clinical manifestations of endogenous endophthalmitis, most ophthalmologists could misdiagnose it as uveitis, and glucocorticoid or immunosuppressive agents would be administrated, which would aggravate the development of the disease. This situation requires the doctor to make the diagnosis of the disease from the perspective of integrative medicine, i.e., make sure not to neglect the patient's systemic history on the basis of the patient's ocular performance. At the same time, X-ray, CT, magnetic resonance, ultrasonic examination, and blood culture could be performed on the patients, and if infected lesions in other

parts of the whole body could be found by these examinations, it would be really helpful for the diagnosis of the disease.

34.6 Treatment for Endogenous Endophthalmitis

Drug treatment mainly includes focal and systemic therapy, antibacterial or antifungal. For endogenous fungal endophthalmitis, amphotericin B commonly serves as the first choice. Fluconazole and voriconazole, a new type of antifungal drug, both have a good antifungal effect [23–26]. The required time of systemic medication application ranges from 6 to 8 weeks [27], and shall not be less than 3 weeks. Glucocorticoid is allowed to be applied topically to control the inflammatory response, while systemic administration of it is forbidden. Antifungal agents usually cause renal toxicity, liver toxicity, or blood toxicity. Therefore, during the course of medication, liver function, renal function, and blood tests are required regularly. Antibiotics are applied empirically for endogenous bacterial endophthalmitis, and are adjusted according to the results of antibiotic sensitivity test on the bacteria. Systemic glucocorticoid medicine can be applied based on the antibacterial treatment.

Amphotericin B vitreous cavity injection is a choice for endogenous fungal endophthalmitis, and the injection dose is 5–10 μg. For the endogenous fungal endophthalmitis with severe anterior inflammatory response, 1 mg of amphotericin B for subconjunctival injection can be selected every other day, and there should not be more than three times in total. Moreover, it should be noted that the injection site must be changed during the injection, and the injection frequency should be controlled to avoid scleral necrosis. Vancomycin can be administrated as intraocular injection for endogenous bacterial endophthalmitis, with the injection dose as 1.0 mg; for subconjunctival injection, vancomycin 25 mg or tobramycin 20–40 mg could be applied. For endogenous bacterial endophthalmitis, focal injection can be combined with dexamethasone 2–3 mg.

Vitrectomy should be given to patients with severe endophthalmitis. Timely vitrectomy treatment can directly remove the foci, pathogens, toxins, and turbid vitreous body, coping with possible complications, which can rescue part of useful vision [27–29]. Of 24 cases (32 eyes) with endogenous endophthalmitis of patients from Beijing Tongren Hospital statistics, 22 eyes (68.7%) already had severe visual acuity loss and severe vitreous opacity before the treatment, which made it difficult to observe the fundus, and thus direct vitrectomy treatment was applied. For the remaining 10 eyes (31.3%) with fundus observed, drug treatment was applied, and the symptoms of only 1 case (1 eye) were controlled. The remaining patients had no remission or even became worse, and then vitrectomy was given. For patients combined with severe anterior inflammation, combined lensectomy is suggested. For patients with more serious intraocular inflammation, silicone oil tamponade is recommended regardless of retinal tear holes, as silicone oil has a certain inhibitory effect on the proliferation of microorganisms.

34.7 Prognosis of Endogenous Endophthalmitis

Vision prognosis is usually poor. Diagnosis on early stage and timely use of effective antibiotics or antifungal drugs, combined with vitrectomy, may save the patient's vision. In the previous reports, the prognosis of endogenous bacterial endophthalmitis was significantly worse than that of fungal endophthalmitis. Okada et al. reported that 78% of endogenous bacterial endophthalmitis had a visual acuity lower than 20/400 [21], and Jackson et al. reported that 69% of endogenous bacterial endophthalmitis had visual acuity lower than the finger count, while 25% resulted in eyeball extraction [2]. Endogenous fungal endophthalmitis reported by Leibovitch et al. had a better prognosis that is higher than 20/200 in 62.5% of patients [15]. Binder et al. reported that 84.6% of patients had visual acuity better than 20/200 caused by Candida endophthalmitis, which was significantly higher than that caused by *Aspergillus* [4].

For 24 cases (32 eyes) of endogenous endophthalmitis from Beijing Tongren Hospital, the follow-up observation on prognosis of patients was performed, of which the shortest period is 1 month, and up to 13 months as the longest, with an average of 6.2 months. 19 eyes (59.3%) had improved visual acuity, which was preferably up to 0.4. There were 6 eyes (18.7%) that maintained the original vision after treatment, and four oculars (12.5%) with decreased visual acuity and three oculars (9.4%) ended up in eyeball extraction. The diagnosed period for the patients with good visual prognosis is generally shorter, from 10 days to 1 month.

34.8 Summary

Patients with endogenous endophthalmitis patients often suffer from diseases or factors that can cause the compromised systemic immune function. Fungi are commonly observed as pathogenic microorganisms, especially *Candida albicans*, while *Klebsiella pneumoniae* is more common for bacteria. Diagnosis on early stage and timely application of effective drug that combined with vitrectomy may save the patient's visual acuity.

References

1. Connell PP, O'Neill EC, Fabinyi D, et al. Endogenous endophthalmitis: 10-year experience at a tertiary referral centre. Eye (Lond). 2011;25(1):66–72.
2. Jackson TL, Eykyn SJ, Graham EM, et al. Endogenous bacterial endophthalmitis: a 17-year prospective series and review of 267 reported cases. Surv Ophthalmol. 2003;48(4):403–23.
3. Chung KS, Kim YK, Song YG, et al. Clinical review of endogenous endophthalmitis in Korea: a 14-year review of culture positive cases of two large hospitals. Yonsei Med J. 2011;52(4):630–4.
4. Binder MI, Chua J, Kaiser PK, et al. Endogenous endophthalmitis: an 18-year review of culture-positive cases at a tertiary care center. Medicine (Baltimore). 2003;82(2):97–105.
5. Lim HW, Shin JW, Cho HY, et al. Endogenous endophthalmitis in the Korean population: a six-year retrospective study. Retina. 2014;34(3):592–602.
6. Pinna A, Cara F, Zanetti S, et al. Endogenous Rhodotorula minuta and Candida albicans endophthalmitis in an injecting drug user. Br J Ophthalmol. 2001;85(6):759.
7. Chhablani J. Fungal endophthalmitis. Exp Rev Anti Infect Ther. 2011;9(12):1191–201.
8. Schiedler V, Scott IU, Flynn HW. Culture-proven endogenous endophthalmitis clinical features and visual acuity outcomes. Am J ophthalmol. 2004;137(4):725–31.
9. Chen KJ, Wu WC, Sun MH, et al. Endogenous fungal endophthalmitis: causative organisms, management strategies, and visual acuity outcomes. Am J Ophthalmol. 2012;154(1):213–4.
10. Arevalo JF, Jap A, Chee SP, et al. Endogenous endophthalmitis in the developing world. Int Ophthalmol Clin. 2010;50(2):173–87.
11. Sridhar J, Flynn HW Jr, Kuriyan AE, et al. Endogenous fungal endophthalmitis: risk factors, clinical features, and treatment outcomes in mold and yeast infections. J Ophthalmic Inflamm Infect. 2013;3(1):60.
12. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis. 2000;30(1):14–8.
13. Congrong L, Shaohua P, Dong L, et al. A hospital acquired infection of deep fungus: a clinical investigation and drug resistance. Chin J Nosocomiol. 2002;12(7):485–7.
14. Pfaller MA, Messer SA, Hollis RJ, et al. Trends in species distribution and susceptibility to fluconazole among blood steam isolates of Candida species in the United states. Diagn Microbiol Infect Dis. 1999;33(4):217–22.
15. Leibovitch I, Lai T, Raymond G, et al. Endogenous endophthalmitis: a 13-year review at a tertiary hospital in South Australia. Scand J Infect Dis. 2005;37(3):184–9.
16. Wong JS, Chan TK, Lee HM. Endogenous bacterial endophthalmitis. An east Asian experience and a reappraisal of a severe ocular affliction. Ophthalmology. 2000;107(8):1483–91.
17. Peizeng Y. Clinical uveitis. Beijing: People's Medical Publishing House; 2004. p. 677–8.
18. Cornut PL, Chiquet C. Endogenous bacterial endophthalmitis. J Fr Ophthalmol. 2011;34(1):51–7.
19. Lee JH, Kim JS, Park YH. Diagnosis and treatment of postpartum Candida endophthalmitis. J Obstet Gynaecol Res. 2012;38(9):1220–2.
20. Tanaka M, Kobayashi Y, Takebayashi H, et al. Analysis of predisposing clinical and laboratory findings for the development of endogenous fungal endophthalmitis: a retrospective 12-year study of 79 eyes of 46 patients. Retina. 2001;21(3):203–9.
21. Okada AA, Johnson RP, Liles WC. Endogenous bacterial endophthalmitis. Report of a 10-year retrospective study. Ophthalmology. 1994;101(5):832–8.
22. Greenwald MJ, Wohl LG, Sell CH. Metastatic bacterial endophthalmitis: a contemporary reappraisal. Surv Ophthalmol. 1986;31(2):81–101.
23. Christmas NJ, Smiddy WE. Vitrectomy and systemic fluconazole for treatment of endogenous fungal endophthalmitis. Ophthalmic Surg Lasers. 1996;27(12):1012–8.
24. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis. 1990;12(2):308–29.
25. Akler ME, Vellend H, McNeely DM, et al. Use of fluconazole in the treatment of candidal endophthalmitis. Clin Infect Dis. 1995;20(3):657–64.
26. Riddell J 4th, Comer GM, Kauffman CA. Treatment of endogenous fungal endophthalmitis: focus on new antifungal agents. Clin Infect Dis. 2011;52(5):648–53.
27. Penk A, Pittrow L. Status of fluconazole in the therapy of endogenous Candida endophthalmitis. Mycoses. 1998;2:41–4.
28. Michal W, Olena W, Wojciech O. Bilateral endogenous fungal endophthalmitis. Int Ophthalmol. 2014;34(2):321–5.
29. Shen X, Xu G. Vitrectomy for endogenous fungal endophthalmitis. Ocul Immunol Inflamm. 2009;17(3):148–52.

Part VIII

Surgery and Ophthalmopathy

Surgical Treatment of the Orbicularis Oculi Muscle Spasm and Supraorbital Neuropathy

35

Yanbing Yu, Li Zhang, and Jian Wu

35.1 Introduction

The orbit and ocular muscles are innervated by the ophthalmic branches of the trigeminal nerve and are closely related to the facial nerve and the trigeminal nerve. Functional neurological diseases, such as spasticity, pain, and paralysis, often show ocular symptoms as its idiopathic manifestations. Orbicularis oculi muscle spasm and ocular pain caused by various factors are one of the diagnostic difficulties for ophthalmologists. This section integrates neurosurgery knowledge, and describes the pathogenesis, clinical manifestations, and treatment of the orbicularis oculi muscle spasm, orbicularis muscle spasm after Bell's palsy, and supraorbital neuralgia. After reading this chapter, the ophthalmologists can know the special examinations and differential diagnosis of the neurology related to ophthalmology. Meanwhile, it is suggested that ophthalmologists should pay attention to differentiate the orbicularis oculi muscle spasm and eye pain from those caused by other factors. At the same time, the drug treatment, surgical indications, and postoperative complications of orbicularis oculi muscle spasm and supraorbital neuralgia are also introduced, aiming to help ophthalmologists to promptly make the correct diagnosis and cooperate with the neurologist in the clinical work.

As the most rapid developing subspecialty in the field of neurosurgery, functional neurosurgery has made a considerable progress in recent years. The diseases belonging to treatment range of functional neurosurgery mainly include cranial nerve disorders, epilepsy, pain, dyskinesia, spasticity, etc. Among them, idiopathic hematologic spasm (HFS) and primary trigeminal neuralgia (TN) in cranial nerve disorders are closely related to ophthalmic diseases. This chapter focuses on the surgical treatment of the orbicularis oculi muscle spasm and supraorbital neuralgia, in order to help the diagnosis, differential diagnosis, and treatment of related diseases.

35.2 Orbicularis Oculi Muscle Spasm

Orbicularis oculi muscle spasm is a manifestation of idiopathic HFS. Idiopathic HFS is manifested as paroxysmal and involuntary spasmodic twitch of the facial muscle on one side of the face. At the beginning of the disease, it can be seen in the upper and lower eyelids, which is characterized by intermittent twitching of the orbicularis oculi, with slow development, and then gradual extending to all the muscles of the side of the face. The eyes cannot be opened in severe cases. It is rare to attack from the corner of the mouth and develop upward reversely. HFS on both sides is very rare, often attacking on one side, and then extending to the other side; in addition, the state of one side is heavier. In general, HFS cannot be self-healing, and the patient is unable to control his or her spasms, often with obvious symptoms in the case of being tense and tired, or meeting strangers, appearing in public places. There is no positive sign of nervous system. Part of patients show peripheral facial paralysis caused by prolonged illness or injection of botulinum toxin. There are no positive findings in the laboratory examination. Imaging examinations such as head CT and MRI are helpful in finding out secondary causes (Fig. 35.1). By thin-layer scanning of the posterior cranial fossa MRA, it can be seen sometimes that blood vessels are adjacent to or even compress the facial nerve root on the involved side (Fig. 35.2).

Due to the missed diagnosis and misdiagnosis of HFS and the lack of population base for statistics and other reasons, its epidemiological reports are still very rare. Auger and

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_35

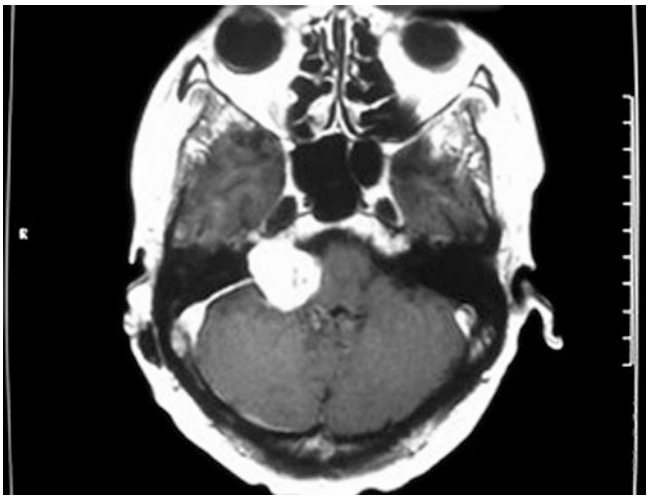

Fig. 35.1 Left hemifacial spasm patients, preoperative MRI showed left acoustic neuroma

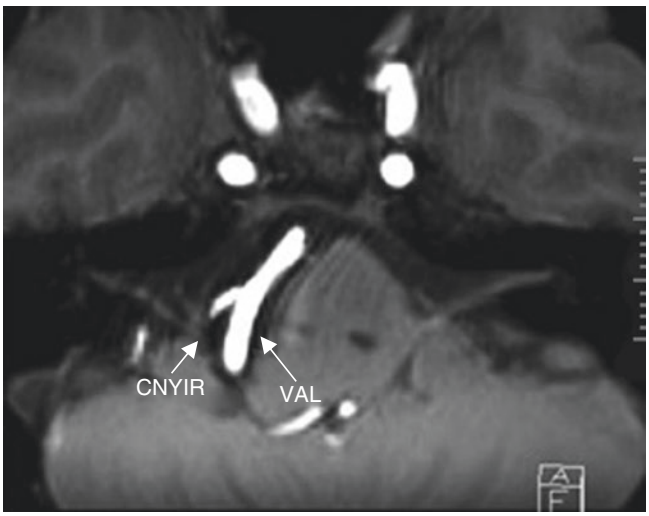

Fig. 35.2 Left hemifacial spasm patients, preoperative MRA showed vertebral artery compressing facial nerve root

Whisnant [1] conducted a statistical analysis for the 24-year incidence of HFS in some parts of the United States from 1960 to 1984, and found that the incidence of male HFS was 7.4/100,000 and the incidence of female HFS was 14.5/100,000, which was common in the 40- to 79-year-old people. Dietrichs et al. [2] reported that in Norway, the incidence of HFS was 9.8/100,000; and the prevalence rates were increased in people above 39.7 years old. Although there is no research on the incidence of Asian populations, it is generally believed that it may be higher than that of Westerners.

Because the clinical manifestations of idiopathic HFS usually involve the involuntary convulsive spasm of the orbicularis oculi muscle, a significant number of patients will be first seen in ophthalmology. Therefore, the differential diagnosis of HFS and other ophthalmic diseases is very important, and the following diseases should be identified clinically: (1) Habitual blepharospasm: This disease is mainly manifested as transient and paroxysmal small spasm of bilateral eyelid, with the parts lower than eyelids unaffected. It is often more common in childhood and adolescent, and can be controlled by consciousness. (2) Hysterical blepharospasm: This disease is mainly manifested as paroxysmal and involuntary spasm of bilateral eyelid, with the parts lower than eyelids unaffected and longer onset time. It is more common in young or middle-aged women, and accompanied by other manifestations of hysteria, with relevance to many mental factors. The suggestive therapy is effective for the disease. (3) Orbicularis oculi muscle twitching: This disease is mainly manifested as the small tremor of the orbicularis oculi muscle bundle, often with one side affected. It can be relieved spontaneously for a period of time, possibly due to the stimulation of xerophthalmia or the benign lesion of the cerebral nerve. In addition, some movement disorders involve the extrapyramidal system, which can also have complicated and changeable ocular manifestations: (1) Some extrapyramidal diseases such as chorea and athetosis can be accompanied by the involuntary twitch of the orbicularis muscle, which is bilaterally and simultaneously with the involuntary movement of the limbs. (2) Meige syndrome is also known as idiopathic blepharospasm—oromandibular dystonia syndrome, manifested as involuntary spasm of bilateral eyelid complicated by orofacial and tongue abnormal movements, and often accompanied by mental disorders, depression, or anxiety. Electromyogram shows that the discharge of facial muscles is not synchronous, but with normal frequency. Such patients can be instructed to visit the neurosurgery after the ophthalmology clinical initial diagnosis, and the neuromodulation therapy such as deep brain stimulation (DBS) has good therapeutic effect. When clinical physical examination is insufficient to diagnose, electrophysiological examination of the facial nerve is essential for the differential diagnosis of HFS. Abnormal muscle response (AMR) on affected side is a unique objective electrophysiological index of idiopathic HFS patients; that is, to stimulate a branch of facial nerve, the abnormal electromyography reaction can be recorded in facial muscles dominated by another branch. The diagnosis of HFS can certainly be established when AMR typical abnormal waves are monitored on the affected-side muscles.

The pathogenesis of idiopathic HFS is that demyelination lesions occur in root exit zoom (REZ) of the facial nerve because of being oppressed by offending vessel. Therefore, microvascular decompression (MVD) of the facial nerve root is the only possible way to cure HFS by detecting with entering the cerebellopontine angle (CPA) via retrosigmoid approach [3]. Surgical indications include the following: (1) Idiopathic HFS without any secondary lesion; (2) no facial nerve injury and Bell's palsy history; and (3) no serious sys-

temic disorder. Via a small-incision keyhole approach behind the affected ear, the hard membrane is opened to probe the CPA and the facial nerve REZ, and the arachnoid around the offending vessels is fully dissected. The offending vessels pass through the facial nerve REZ with mostly appearing in loop structure and cause oppression. Common offending vessels are as follows: anterior inferior cerebellar artery trunk and (or) branch (38.6–65%) > posterior inferior cerebellar artery trunk and (or) branch (15.3–50%) > vertebral artery (17–25%) > multiple arteries' co-oppression (4.2–19%). When the offending vessels are fully free, they are pushed toward the skull to leave REZ, and the cushions are placed between the blood vessels and the brain stem (Figs. 35.3 and 35.4).

The efficiency of MVD can reach more than 95% for the treatment of HFS. The postoperative facial palsy on the affected side is a major complication, which can occur immediately or within 2 weeks after operation [4]. The incidence of this complication is 1–5%, mostly resulted from the mechanical damage of the facial nerve or blood supply affected during the operation. Severe postoperative facial palsy on the affected side can cause ipsilateral eyelid closure insufficiency, thus easily leading to the exposure conjunctivitis or corneal damage. The measures such as using eye drops, applying eye ointment, and covering the exposed conjunctiva are needed to be taken. Most facial palsy can be restored to normal state within 2–6 months after operation. Diplopia is also a common complication after MVD operation, mostly manifested as binocular diplopia. In general, it is caused by stimulation of the abducent nerve or trochlear nerve during the CPA exploration process. Diplopia is usually reversible, and the symptoms can be relieved within 3 months with no special treatment.

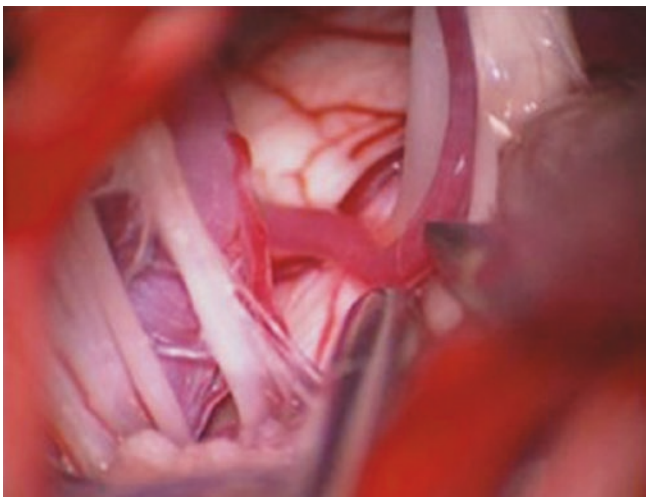

Fig. 35.3 Left hemifacial spasm patients, facial nerve root was found to be compressed by the posterior inferior cerebellar artery branch

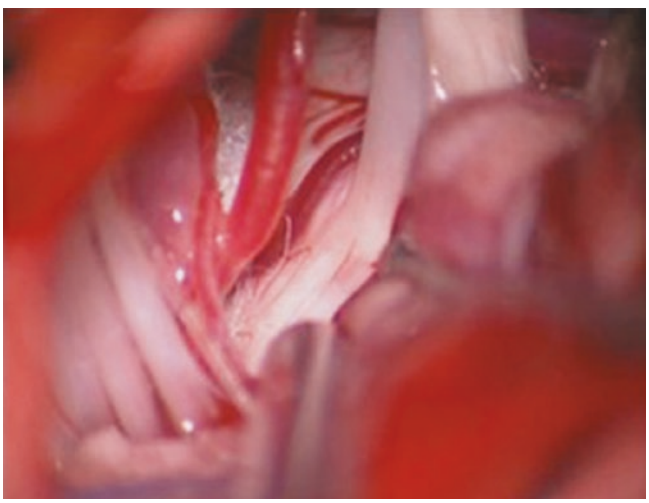

Fig. 35.4 The posterior inferior cerebellar artery branch was removed from the facial nerve root with cotton pad

35.3 The Orbicularis Oculi Muscle Spasm After Bell's Palsy

Bell's palsy, which is defined as an acute and idiopathic unilateral peripheral facial nerve palsy, is a self-limited, non-progressive, self-relieved, and non-life-threatening disease [5]. In 1821, British neurologist Bell first described the clinical manifestations of the disease, which is characterized by acute onset, with more than a few hours or 1–3 days to reach the peak, and generally manifested as follows: ipsilateral mouth drooping, upper and lower lip unable to be tightly closed, unable to bulge the cheeks and blow, eyelids on the affected side unable to be completely closed to expose the conjunctiva, and disappearance of forehead wrinkles on the affected side. In addition, the patient cannot frown, and has taste, hearing, saliva, and tear secretion disorders. The characteristic ophthalmic sign is that when the eyes are closed, the eyeball on the affected side turns to the upper inner, exposing the white sclera below the cornea, which is called Bell phenomenon. The incidence of Bell's palsy was 20/300,000–30/300,000, and there was no significant difference between men and women, with the median age of 40 years. After the combined treatment of hormone, antiviral drugs, and neurotrophic drugs, most of the patients can recover the facial muscle function completely. During the treatment, special attention should be paid to the protection of the conjunctiva. Some patients have left sequelae, including facial muscle fiber tremor, synkinesis, facial atrophy, and abnormal facial sensation. Among them, the facial muscle fiber tremor, synkinesis, and others can be collectively called facial nerve hyperexcitability sequela after Bell's palsy.

The orbicularis oculi muscle spasm after Bell's palsy is a manifestation of idiopathic HFS after Bell's palsy. The idiopathic HFS after Bell's palsy was defined as the ipsilateral

HFS that emerged after the complete cure of Bell's palsy, which is not a common disease in clinic. Unlike facial nerve hyperexcitability sequela after Bell's palsy, the clinical manifestation of HFS after Bell's palsy is equivalent to the typical idiopathic HFS without the history of Bell's palsy. The facial muscle fibrillation after Bell's palsy is characterized by slight, small tremor in the facial muscles, especially common in the orbicularis oculi muscle. The facial synkinesis after Bell's palsy is manifested as abnormal involuntary movements of the other muscle resulted from the voluntary movement of one facial muscle, clinically showing the involuntary movements of the eye muscles caused by involuntary angular movements or movements of the mouth when the eyes are closed, which should be paid attention in the differential diagnosis in ophthalmology. The importance of differential diagnosis is that HFS after Bell's palsy can be cured by MVD, but the treatment of facial nerve hyperexcitability sequela after Bell's palsy is poor and noneffective [6].

In many cases, however, it is difficult for doctors to accurately identify HFS after Bell's palsy and facial nerve hyperexcitability sequel after Bell's palsy, especially the orbicularis oculi muscle spasm with mild symptoms and the heavier orbicularis oculi muscle spasm fibrillation or the synkinetic movements with frequent occurrence. The key to differential diagnosis depends on the detailed inquiry of patient's previous medical history; HFS after Bell's palsy must appear after a period of time when the Bell's palsy was completely cured, and this time can range from a few months to several years. However, facial nerve hyperexcitability sequel after Bell's palsy does not have this healing period when clinical manifestations are completely normal. In addition, the ipsilateral facial muscle AMR is a special objective electrophysiological index for patients with idiopathic HFS, which cannot be detected in the normal population and in patients with facial nerve hyperexcitability sequel after Bell's palsy, so it has accurate diagnostic value [7].

35.4 Supraorbital Neuralgia

Supraorbital neuralgia is the pain in ophthalmic branch (the first branch) of the primary trigeminal nerve (TN). The primary TN is mainly characterized by recurrent and paroxysmal severe pain in the trigeminal area of one side of the head and face. Most of the pain is unilateral, with a sudden severe facial pain like tearing pain, electric shock pain, acupuncture pain, knifelike pain, or burning pain, characterized by sudden onset and sudden cessation. Trigger points are located in the upper and lower lips, nosewing, nasolabial groove, gingiva, cheek, mouth, tongue, eyeball, and so on. The pain can be induced in the case of being tense and anxious, and having facial mechanical stimulation or facial movements, which is common in sneezing, laughing, chewing, turning, eating, drinking water, wind blowing, cold, brushing teeth, washing face, talking, yawning, and shaving. Some patients may be accompanied by lachrymation from the affected eye or binocular eyes, pupil expansion, conjunctival hyperemia, and other eye symptoms. The pain range of the supraorbital neuralgia is involved with the forehead area above the palpebral fissure, and a small number of patients showed a pain that was confined to the periocular region. It should be differentiated from some ocular diseases such as glaucoma, iris ciliary inflammation, orbital cellulitis, refractive errors, and imbalance of the eye muscles, which are always accompanied by visual dysfunction.

In more than a half of the primary TN patients, the pain can be effectively relieved by taking orally low-dose carbamazepine and other drugs for a long term. Carbamazepine is now the most accurate and commonly used drug for the treatment of primary TN, and the efficacy of other drugs is not accurate. The drug mainly acts on the reticular structure—the thalamic system—by inhibiting the pain of pathological polyneuronal reflex to relieve symptoms. The initial dose is 100 mg/day, and the maximum dose should not exceed 1000 mg/day. A considerable number of patients cannot tolerate the side effects of the drug and seek other treatments. The main side effects include drowsiness, dizziness, gastrointestinal reaction, ataxia, liver loss, and leukocyte reduction.

For the TN that is ineffective for conservative treatment, the CPA probing via the retrosigmoid approach and the MVD of the trigeminal nerve root are the first choices for surgical treatment. Surgical indications are as follows: (1) primary TN patients, excluding secondary lesions; (2) patients with poor effect of conservative treatment or unable to tolerate the side effects of medicine or with liver damage caused by taking medicines; and (3) patients with no severe systemic disease and no strict limits on age. Via a small-incision keyhole approach behind the affected ear, the hard membrane is opened to probe the CPA and the trigeminal nerve REZ, and the arachnoid around the trigeminal nerve root is fully dissected. Arachnoid thickening and adhesion may be a pathogenic factor of TN, which should be fully dissected from the brain stem to the bursa of Fabricius, so that the trigeminal nerve root can be completely loosened in the axial position. Then, the head of the patient is rotated 15° backward or the axis of the operating microscope is adjusted to expose the trigeminal nerve REZ. Common offending vessels include the superior cerebellar artery trunk and branches, the anterior inferior cerebellar artery trunk and branches, the basilar artery, and the lava vein branch (Fig. 35.5). Any blood vessel in contact with the lateral pontine segment of the trigeminal nerve should be treated as an offending vessel and must be treated. When the offending vessels are fully free, they are pushed inwards or toward the tentorium or skull base to leave REZ, and the cushions are used to separate. The

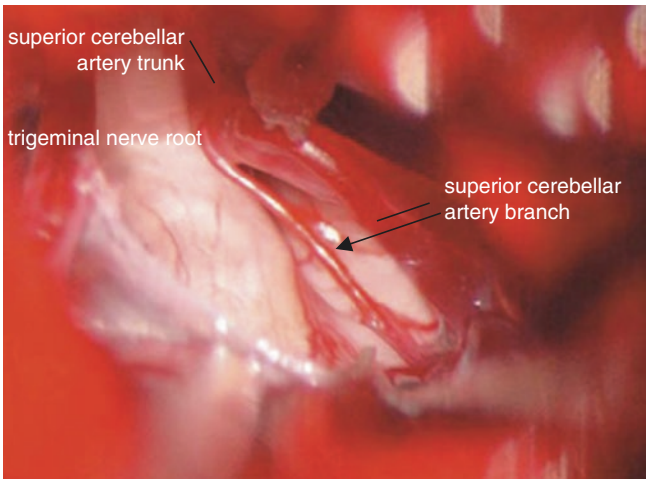

Fig. 35.5 Left trigeminal neuralgia patients, the trigeminal nerve was found to be compressed by the superior cerebellar artery trunk and branch in surgery

cure rate of MVD for primary TN is 65–80%; the ineffective rate is 1–20%; and the recurrence rate is 3–15%. The partial rhizotomy (PR) of sensory root of trigeminal nerve will often be performed if the offending vessel is not found during the course of the exploration. The proportion of the cut should not exceed 3/4, and the first sensory root fiber in the top part should not be cut off so as not to affect the corneal sensation.

The postoperative corneal sensory disturbance caused by the damage in the ophthalmic branch nerve fiber of the sensory root of the trigeminal nerve can be seen occasionally, and usually occurs after the sensory root rhizotomy, with a few caused by postoperative hemorrhage of the posterior fossa. The fiber of ophthalmic branch of the trigeminal nerve conducts important corneal sensation, and once being injured may cause corneal sensory disappearance, blink function decrease, and possibly corneal infection. The complications are characterized by local painlessness, no stimulation, and other self-conscious symptoms. In the early stage, only conjunctival congestion, corneal sensation loss, epithelial edema, and punctate opacities can be found. Then, some corneal vesicles are present and the central epithelium of the cornea desquamates and develops around the cornea. Finally, there are only a few epitheliums in the annular corneal margin, and the coloboma area is dry and milky white. If the infection continues to develop, it can rapidly cause the anterior chamber to accumulate pus and lead to the corneal perforation, and it is often associated with iris inflammation, which may require eyeball extraction for the severe cases. When partial rhizotomy (PR) of sensory root of trigeminal nerve is decided to be performed, it is necessary to strictly control the cut ratio [8], and do not injure the sensory fiber of ophthalmic branch of the trigeminal nerve. The corneal sensation examination should be conducted in time after operation. Once corneal reflexes have disappeared or the signs of keratitis have been found, the cornea should be immediately protected by using eye drops, applying eye ointments, wearing goggles or windproof glasses, or covering the affected eye wetly and by other measures. If the cornea has been ulcerated, the eye crack can be sutured temporarily or for a long time according to the condition of the disease, so as to prevent the further development of corneal lesions.

PR is not suitable for supraorbital neuralgia. Supraorbital nerve avulsion may be used in patients with supraorbital neuralgia who cannot tolerate MVD or have no effect for MVD. The operation is performed under local anesthesia, with the incision in the eyebrows, and the incisura supraorbitalis is revealed after the incision, and then the supraorbital nerve can be torn off. The operation has a high recurrence rate, but it can be repeated.

References

1. Auger RG, Whisnant JP. Hemifacial spasm in Rochester and Olmsted County, Minnesota, 1960 to 1984. Arch Neurol. 1990;47(11):1233–4.
2. Nilsen B, Le KD, Dietrichs E. Prevalence of hemifacial spasm in Oslo, Norway. Neurology. 2004;63(8):1532–3.
3. Barker FG, Jannetta PJ, Bissonette DJ, et al. Microvascular decompression for hemifacial spasm. J Neurosurg. 1995;82:201–10.
4. Ishikawa M, Nakanishi T, Takamiya Y, et al. Delayed resolution of residual hemifacial spasm after microvascular decompression operations. Neurosurgery. 2001;49(4):847–54.
5. Gilden DH. Clinical practice: Bell's Palsy. N Engl J Med. 2004;351(13):1323–31.
6. Valls-Sole J. Facial palsy, postparalytic facial syndrome, and hemifacial spasm. Mov Disord. 2002;17(Suppl 2):49–52.
7. Valls-Sole J. Electrodiagnostic studies of the facial nerve in peripheral facial palsy and hemifacial spasm. Muscle Nerve. 2007;36(1):14–20.
8. Steven N, Emad N, Boo S, et al. Microvascular decompression surgery in the United States, 1996 to 2000: mortality rates, morbidity rates, and the effects of hospital and surgeon volumes. Neurosurgery. 2003;52(6):1251–62.

Surgical Treatment of Ocular Myasthenia Gravis

36

Lei Yu and Jian Wu

36.1 Introduction

Myasthenia gravis is a disorder of neuromuscular transmission which is related to acetylcholine (Ach) deficiency. The initial symptoms are common in the eyes with acute onset, including ptosis, diplopia, and extraocular muscle paralysis. The lesions are merely in the eyes without involvement of other nerves, which is called ocular myasthenia gravis (OMG). OMG may not develop into systematic disease in most cases. Thus, the ocular myasthenia gravis patients may usually present to the ophthalmologist for treatment. As a result, it is necessary for the ophthalmologist to master the pathogenesis, clinical manifestation, diagnostic criteria, and treatment of myasthenia gravis, and to differentiate it from other neurological diseases, so as to render accurate diagnosis and treatment plan promptly. In this section, we have a systematic introduction of clinical symptom, differential diagnosis, and drug therapy of OMG from the surgical prospective. At the same time, the approach, prognosis of thymectomy for myasthenia gravis, and application of minimal invasive surgery are introduced in detail, and the related symptoms and treatment methods of myasthenia gravis complicated by thymoma are also discussed, which can provide new ideas about the treatment of OMG for the ophthalmologist.

Myasthenia gravis (MG) is an autoimmune disease that is caused by the transmission function disorder of the neuromuscular junction, clinically manifested as partial or generalized skeletal muscle weakness and fatigability. The symptoms are exacerbated after activities, and relieved with a break. The prevalence rate ranges from 77/1,000,000 to 150/1,000,000, and the annual incidence is 4/1,000,000–11/1,000,000. MG is reported more commonly in females than males, with the ratio of 3:2. There is no difference between ages in the incidence.

36.2 Pathogenesis

Myasthenia gravis is mainly an autoimmune disease affecting acetylcholine receptors (AChR) on postsynaptic membrane of neuron-muscular junctions, involved with AchR antibody-mediated humoral immunity, T-cell-mediated cellular immunity, and complement. For years, a multitude of researches on pathogenesis of myasthenia gravis have been carried out, fully confirming the importance of immune mechanism in the course of MG. However, there are still many phenomena in the etiology of MG that cannot be explained by immunologic mechanism. Although antiacetylcholine receptor antibodies (AchRAb) can be detected in serum for above 85% of patients with myasthenia gravis, AchRAb is negative in serum for minority of MG patients. Moreover, the discovery of a variety of non-AchR antibodies in some serum of MG patients demonstrates that some non-AchR antibodies and muscle-specific protein changes may also play a significant role in the morbidity and development of MG apart from AchR antibodies. Besides, certain genetic predisposition and susceptibility have been found in the morbidity of MG, which are related to HLA phenotype, AchR α-subunit gene, immunoglobulin heavy-chain gene, and T-cell receptor gene. Thymus is a vital factor in activating and maintaining the autoimmune reaction of myasthenia gravis patients. Up to 65–80% of MG patients have thymic hyperplasia, and 10–20% of MG patients are complicated by thymoma, which may not appear in young patients.

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_36

36.3 Clinical Features

MG patients may often feel swollen and uncomfortable in eyes and limbs, or blurred vision, fatigue, hot weather, or menstrual onset-aggravated fatigue in the early stage. 30–40% of patients complain of a history of upper respiratory tract infection about 1–2 weeks before being sick. With the development of the disease, the patients show obvious fatigue and weakness in skeletal muscles, with a distinguishing feature that the myasthenia is exacerbated after activities in the afternoon and evening, and relieved in the morning or with a break. Besides, myasthenia gravis is typically characterized by easily fatigue, and the muscles gradually become weak during activities, which can be back to normal after a period of rest.

36.3.1 Clinical Symptoms

Skeletal muscle of the whole body can be involved in myasthenia gravis patients. Depending on the muscle involved, patients may have the symptoms as follows:

1. Blepharoptosis, blurred vision, diplopia, strabismus, inflexible eye movements
2. Apathy, sardonic feature, big tongue, enunciation unclear, dysarthria, often accompanied by snuffle
3. Weakness of chewing, choking, dysphagia
4. Soft neck, difficult to head-up, neck rotation, weak in shrugs
5. Difficult to lift up arms, comb hair, climb stairs, squat, get on or off

36.3.2 Clinical Classification

Myasthenia gravis is often complicated by autoimmune diseases such as hyperthyroidism, rheumatoid arthritis, lupus erythematous, polymyositis, and multiple sclerosis. At present, there are two types of myasthenia gravis:

36.3.2.1 The Type of Improved Osserman

(1) Type I: eye muscle; (2) type IIA: MILD systemic weakness, limb muscles often accompanied by eye muscle involvement, without presentation of pseudo-bulbar palsy such as no weakness of chewing and swallowing or dysarthria; (3) type IIB: limb muscles often accompanied by eye muscle involvement, with presentation of pseudo-bulbar palsy, most showing dyspnea in half a year; (4) type III: severe radical type, with rapid onset, most progressed to dyspnea in several weeks or months; (5) type IV: delayed severe type, most progressed from type I, type IIA, and type IIB in 2 years. (6) type V: muscle atrophy, which is uncommon.

36.3.2.2 The Type of Myasthenia Gravis Foundation of America (MGFA)

I. Occurrence of ocular weakness or fatigue, blepharoptosis probability; there is no other evidence of muscle weakness or fatigue in rest of the body.
II. The ocular weakness or fatigue is slightly serious, and other muscle weakness or fatigue in rest of the body is in mild condition
   A. Mainly at limb or trunk muscle
   B. Mainly at bulb muscle and/or respiratory muscle
III. The ocular weakness or fatigue is serious, with other muscle weakness or fatigue in rest of the body
   A. Mainly at limb or axial muscle.
   B. Mainly at bulb muscle and/or respiratory muscle.
IV. The ocular weakness or fatigue is serious, and other muscle weakness or fatigue in rest of the body is serious.
   A. Mainly at limb or trunk muscle
   B. Mainly at bulb muscle and/or respiratory muscle (need to feed in a throat, but not necessary to intubate)
V. Necessary to intubate to keep breathing.

36.3.3 Myasthenic Crisis

Myasthenic crisis refers to the dyspnea and life-threatening critical phenomena caused by a sudden rapid exacerbation for some reason in the course of myasthenia gravis. MG crisis is mainly divided into three types according to different reasons, including the following: (1) myasthenic crisis: it is mainly caused by the development of disease, and also could be induced by infection, excessive fatigue, mental stimulation, menstruation, childbirth, surgery, and trauma. Clinical manifestations include the sudden aggravation of MG, appearing of weakness of swallowing and expectoration, expiratory dyspnea, often accompanied by mood irritability, sweating, and other symptoms; (2) cholinergic crisis: it can be seen in patients taking pyridostigmine bromide with long-term high dose, or temporarily overtaking; before the crisis, the patients often present psychotic symptoms such as nausea and vomiting, abdominal pain, diarrhea, sweat, tears, clammy skin, oral secretion increase, fasciculation, and emotional anxiety; (3) brittle crisis: unchanged-dose of pyridostigmine bromide falls into failure and patients appear severe dyspnea; it is also caused by infection, electrolyte disturbance, and other unknown reasons.

Myasthenic crisis is the most common one among all the three types, followed by brittle crisis, and the real cholinergic crisis is infrequent. Myasthenic crisis is a critical condition with the mortality of 15.4–50% once setting on.

36.4 Diagnosis

1. Neostigmine test

   The usual dose in adults is 1–1.5 mg, with being administered intramuscularly. The symptoms can be improved within 10–15 min after an injection, and the peak effect is achieved in 30–60 min; at the same time, the duration time of effect may last for 2–3 h, which means test positive.
2. Chest CT

   Thymic hyperplasia and thymoma can be detected by chest CT. Patients are recommended to be performed enhanced scanning for further definition (Fig. 36.1).
3. Repetitive nerve electrical stimulation

   Repetitive nerve electrical stimulation is a common examination method with diagnostic value. The motor nerve is electrically stimulated with electrodes, and then the muscle action potential amplitude is recorded. If a characteristic decrement in muscle action potential is seen gradually, it will suggest the possibility of pathological changes occurred at neuromuscular joint.
4. Single-fiber electromyography (SFEMG)

   Single-fiber electromyography is a more sensitive diagnostic method for detecting abnormal neuromuscular transmission compared with repetitive nerve electrical stimulation. The abnormalities of neuromuscular transmission can be detected on the basis of the increased jitter when both repetitive nerve electrical stimulations and clinical symptoms are normal. SFEMG has the highest sensitivity among all the examination methods of amyosthenia.
5. AchR-Ab titer test

   AchR-Ab titer test has a characteristic significance for the diagnosis of MG. Antiacetylcholine receptor antibodies can be detected in as many as 80–90% of patients with generalized myasthenia and 60% of patients with OMG. The level of antibody titer is not in complete conformity with the severity of the clinical symptoms.

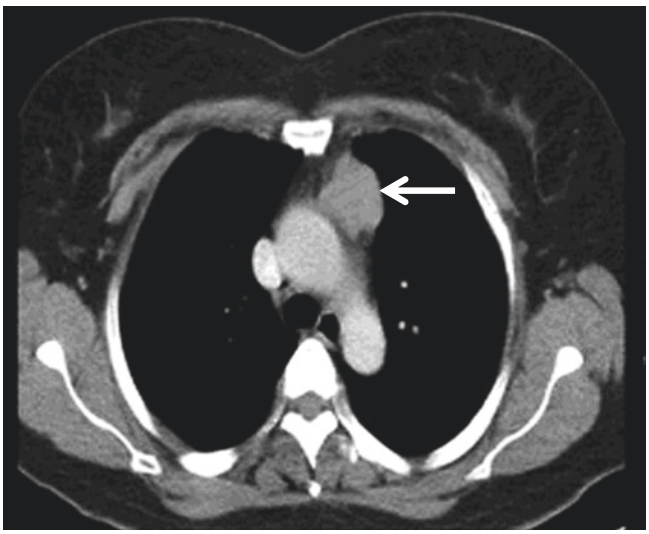

Fig. 36.1 Chest CT shows occupying lesions in the anterior mediastinal

36.5 Treatment

36.5.1 Drug Treatment

1. Cholinesterase inhibitors: Cholinesterase inhibitors are the symptomatic treatment drugs, aiming to cure symptoms instead of the disease, and cannot be long-term application for single drug. These drugs should be increased from a small dose. Commonly used drugs include neostigmine methyl sulfate and pyridostigmine bromide.
2. Immunosuppressive: Commonly used immunosuppressive agents include (a) adrenal corticosteroids, such as prednisone and methylprednisolone; (b) azathioprine; (c) cyclosporine A; (d) cyclophosphate; and (e) tacrolimus.
3. Plasma replacement: By the way of removing acetylcholine receptor antibody in patient's blood, the symptoms of patients with myasthenia gravis are temporarily relieved. If other adjuvant treatments are not adopted, the efficacy will last no more than 2 months.
4. Intravenous immunoglobulin: Human immunoglobulin contains a variety of antibodies, which can neutralize autoantibodies and regulate immune function. The treatment effect is comparable to plasma replacement.
5. Traditional Chinese medicine (TCM) therapy: Chinese traditional treatment of myasthenia gravis has got more and more attention. Myasthenia gravis belongs to "flaccidity syndrome." According to Chinese medicine theory, with the combined treatment of traditional Chinese medicine, it can reduce the side effects of immunosuppressive agents. TCM therapy not only plays an important role of escort for the treatment of myasthenia gravis, but also can rebuild the function of autoimmune function.

36.5.2 Thymectomy

Currently, thymectomy has been generally recognized as an effective method for the treatment of patients with myasthenia gravis. It is reported that the effective rate of operation is 60–80%. The indications for thymectomy include the following: (1) patients above the age of 14 with generalized-type myasthenia gravis and no surgical contraindications (dysfunctions of the heart, brain, lungs, kidney, and other vital organs), and most patients can be significantly improved by thymectomy; (2) myasthenia gravis patients complicated by thymoma; and (3) whether to operate ocular myasthenia gravis patients still remains controversial.

Since the first successful treatment with thymectomy alone for myasthenia gravis operated by Blalock in 1939, it has undergone a series of changes. So far, there have been a number of surgery methods for thymectomy. The MGFA organization divided thymectomy into four categories in 2003, which included (1) transcervical thymectomy (standardized and extended), T-1a and T-1b; (2) thoracoscopic thymectomy (standardized and extended), namely VATS and VATET; T-2a and T-2b; (3) transsternal thymectomy (standardized and extended); T-3a and T-3b; and (4) combined transcervical and transsternal thymectomy, T-4. Academia keeps mixed views on methods, ranges, and prognosis effects of thymectomy.

The specific methods of thymectomy are as follows:

1. Transsternal thymectomy

   The conventional thoracic resection removes thymus and all ten groups of anterior mediastinal fat tissue through median sternotomy in longitudinal, with the operative range from the inferior pole of the thyroid in the neck, down to the diaphragm, and limited in the front edge of hilus pulmonis phrenic nerve on both sides.
2. Thoracoscopic thymectomy (Fig. 36.2)

   According to the characteristics of thymus distribution determined by the preoperative chest CT film, decide to use the right thoracic approach or left approach. Take the right thoracic approach as an example: after the tracheal bicaval intubation, intravenous combined tracheal inhalation anesthesia, the patient is in the posture of the left 45° bed rest, with the thoracoscopy placed in the sixth intercostal space or the fifth intercostal space between the right anterior axillary line and midaxillary line, and the operating holes located in the third intercostal space of the anterior axillary line and the fifth intercostal space of the midclavicular line. Cut open the mediastinal pleura in the gap of vena cava—pericardial ditch, and then separate the internal thoracic vein and the superior cavity venous intersection along the superior vena cava and phrenic nerve (note the protection of the phrenic nerve), with blunt dissection of the lower edge of right lobe thymus. Cut open the mediastinal pleura behind the sternum, with blunt and sharp dissection of the lower pole of the right lobe thymus and extension to the contralateral side (lower pole of left lobe), and then clean up the contralateral pleural and backward to free the right lobe. Dissect the thymus vein along the upper cavity—nameless vein, and cut off after incarceration with titanium clamp. Free the upper pole toward the cervical root to the lower pole of the thyroid, and then dissect the left lobe from the lower pole of left lobe thymus, up to the cervical root, until the lower pole of the thyroid, during which the anterior mediastinal adipose tissue of groups 1–6 and group 10 can be cleared. Finally clear the mediastinal adipose tissue of pericardiac group 7–9, lateral phrenic nerve, and retrosternal area to avoid ectopic thymus tissue residue (Fig. 36.3).

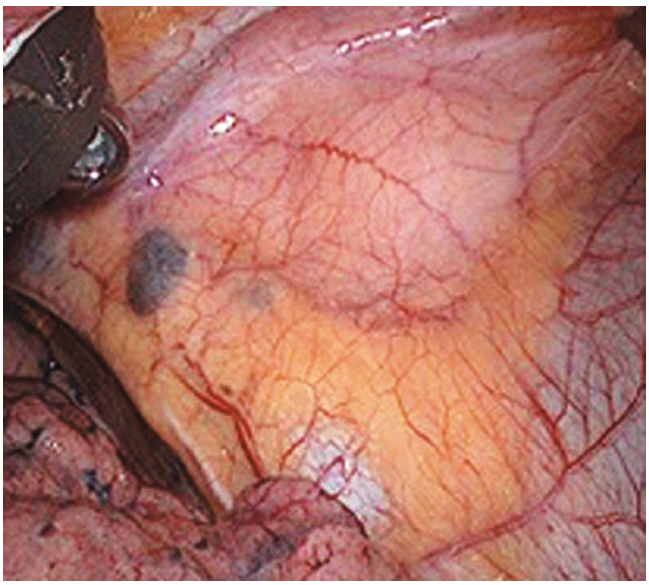

Fig. 36.2 Thymus in the anterior mediastinal under thoracoscopy

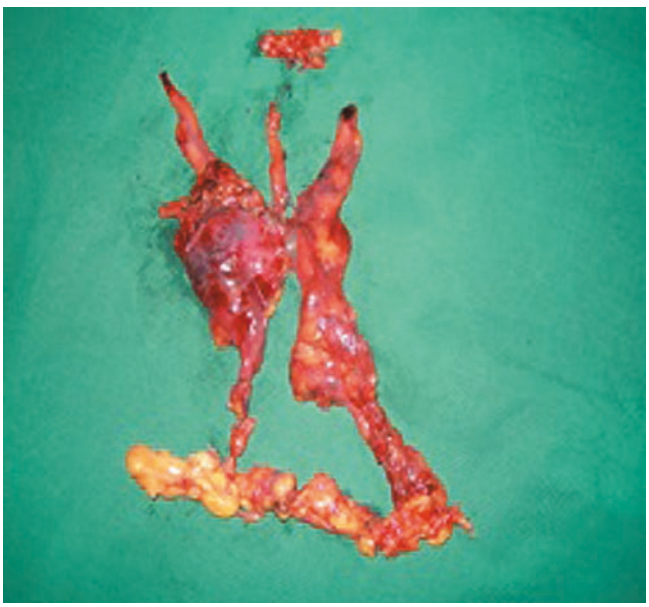

Fig. 36.3 The thymus and cervical root, adipose tissue in the anterior mediastinum excised in extended thymectomy

36.6 Prognosis

Myasthenia gravis patients have a better prognosis, a small number of patients after treatment can be completely relieved, and most patients can maintain the improved symp-

toms by drugs. The vast majority of patients with good efficacy can return to normal learning, work, and life.

36.6.1 Postoperative Efficacy Judgment: MGFA Standard

1. Complete stable remission (CSR): There are no symptoms and signs of myasthenia at least 1 year, and during this period the patients do not receive treatment related to myasthenia. In the assessment of professional neuromuscular disease, any part of the muscle weakness cannot be detected; there may be a simple eyelid closure weakness.
2. Drug remission (PR): In addition to accepting some form of myasthenia treatment, the other standards are same as the CSR. Patients taking cholinesterase inhibitors are excluded.
3. Minor manifestations (MM): Any part of the muscle weakness can be detected in the assessment of the neuromuscular disease.
4. Improve (I): The dosage is reduced or the symptoms of myasthenia are relieved.
5. Unchange (U): There is no change in clinical symptoms.
6. Exacerbation (E): The dosage is increased or the symptoms are aggravated than the preoperative ones, or both.
7. Worsen (W): The symptoms are suddenly worsened after the emergence in the patients.
8. Death.

36.6.2 The Analysis of Operative Effect

Although thymectomy has been recognized as an effective treatment for myasthenia gravis, the means and resection range for thymectomy have been controversial.

These controversies stem from the anatomy of the thymus. The thymus is derived from the three and four pharyngeal pouches, and the ectopic thymus arising from the descent from the neck to the anterior mediastinum can be distributed in the neck, mediastinum, lungs, lung roots, and so on. In 1977, Jaretzki positioned the ectopic thymus in mediastinum, and drew the distribution diagram of thymus tissue in mediastinum in 1988. Ectopic thymus may exist from the cervical root to the diaphragm. Theoretically, thymectomy must achieve the complete excision of the thymus and completely remove the ectopic thymus in the anterior mediastinum and the adipose tissue of the cervical root. There are many ways to perform thymectomy, each of which has its own characteristics and rationality, and that whether the operation is effective or not depends on the removal of thymus tissue and adipose tissue.

Many foreign scholars have tried to compare the mortality, improvement, and long-term effects of the transcervical, transsternal extended thymectomy, but because of the difference of the factors such as the age of the patients, the condition of the drug treatment, the course of disease, and the evaluation criteria, finally they cannot draw a comprehensive and authoritative conclusion. However, all of them consider that the three surgical results are basically similar and the choice of any kind of surgery is reasonable. Jaretzki, who advocated the extended thymectomy, enumerated 15 patients who had relapsed after T-1a and T-3a operation. It was found that there were residual thymus tissues in their secondary surgery with combined transcervical and transsternal thymectomy of T-4, and 13 cases achieved good results after surgery. However supporters of T-1 and T-2 surgery believe that they can also completely remove thymus and ectopic thymus tissue while reducing complications.

In recent years, with the development of minimally invasive thoracoscopic surgery, thoracic surgeons around the world have become more and more interested in thoracoscopic thymectomy. But it also remains a question whether simply thoracoscopic thymectomy can achieve a well exposure of premedial and cervical root, complete excision of the thymus, and thorough removal of the ectopic thymus and adipose tissue in the anterior mediastinum and the cervical root. Many scholars believe that T-3b and T-4 can achieve the requirement of complete excision of thymus and ectopic thymus, and have the desired postoperative effect.

In general, with the time going on after thymectomy, the surgical results will be better for MG patients. Most researchers believe that for the treatment of MG through thymectomy, symptoms have a certain degree of volatility in the short term, with the longer the follow-up period, the better the effect; as long as the recent exacerbation is got through, most can achieve good long-term results. In our study, it was found that AchR antibody changed from positive to negative which was most significant 3–6 months after operation, and the negative conversion rate decreased significantly more than half a year after operation. For many patients with myasthenia, the symptoms were relieved or the dosage was reduced, or was the same as preoperative ones, but physical strength was increased.

But in about 5% of patients with myasthenia gravis, the postoperative symptoms still had no change or were aggravated again after remission; 2–3% of patients were deteriorated or even died. The reasons that the postoperative symptoms of MG had no improvement or were aggravated again after remission were considered as follows: (1) longer course of disease, and Ach-R receptor at neuromuscular junction was permanently and irreversibly damaged; (2) the impact of thymosin, produced by the spleen, lymph nodes, and others except for thymus at which the lymphoid tissue was not resected; (3) longer survival time of AChR antigen-sensitized T lymphocytes, with survival for several years, resulting in the persistence of causal factors in the body; and

(4) heterogeneous disease. Due to the existence of the above factors, even if the resection range is extended, it can only increase the degree of injury to the body with no signicant help on postoperative efficacy. Therefore, in order to block the disease progression, and improve the surgical results, patients with myasthenia gravis should be treated by thymectomy as soon as possible.

36.7 Prevention

36.7.1 Potential Contributing Factors for the Exacerbation or Relapse of Myasthenia Gravis

Common causes are infection, surgery, psychological trauma, systemic diseases, excessive fatigue, female physiological period, pregnancy, delivery, smoking, alcohol consumption, thymoma recurrence, etc.

36.7.2 Caution Medication for MG Patients

1. Antibiotics, such as gentamicin, streptomycin, kanamycin, tetracycline, terramycin, bacitracin, polymyxin, tobramycin, quinolones, and macrolides, should be used with caution.
2. Lipid-lowering drugs.
3. Promethazine, stable, morphine, ether, anesthetic muscle relaxant, procaine, aminoglycoside.
4. Quinine, quinidine, procainamide, wintamin, perphenazine.
5. Ourari, suxamethonium.
6. Thymosin, immunopotentiator.
7. Senso and other proprietary Chinese medicines such as Liushen Pills, Houjiling, and Pearl powder.
8. Avoid giving children with myasthenia gravis an oral liquid available on the market that claims to boost immunity.

36.8 Myasthenia Gravis and Thymoma

Thymoma is one of the most common anterior superior mediastinal tumors derived from thymic epithelial cells. Thymoma is often accompanied with paraneoplastic syndromes, such as hyperthyroidism, simple aplastic anemia, myasthenia gravis, and endocrine diseases, of which myasthenia gravis is the most common one. Domestic and international data show that the incidence of myasthenia gravis (MG) combined with thymoma is basically between 10% and 30%, while the incidence of thymoma combined with myasthenia gravis is between 15% and 60%. In a set of statistics data from Beijing Tongren Hospital, 54.9% of thymoma patients were accompanied with myasthenia gravis, for the reason that most patients were advised to visit Beijing Tongren Hospital after the diagnosis of MG, and the thymoma was found in chest CT. Most thymoma can be surgically resected and the patient could have long-term survival. In the past, it is considered that thymoma combined with MG has many complications and high mortality rate. However, in recent years, some scholars believe that the occurrence of MG is conducive to early diagnosis, with a high success rate of surgical resection, and better prognosis.

Histopathological classification of thymoma combined with myasthenia gravis has its characteristics. Foreign reports demonstrate that the incidence rate of type A thymoma is between 0% and 14%, type AB thymoma between 6% and 42%, type B1 between 7% and 50%, type B2 between 24% and 71%, and type B3 between 25% and 65%. MG is hardly present in thymic carcinoma patients.

The effect of MG on the prognosis of thymoma has always been a hot academic issue. Some scholars believe that the presence of MG is a negative factor in the prognosis of thymoma. It increases perioperative and postoperative mortality by inducing myasthenic crisis and so on. Some other scholars believe that MG is conducive to early diagnosis and beneficial to the prognosis of thymoma. Whether thymoma is accompanied with myasthenia gravis has little effect on its long-term outcome, but with the continuous improvement of MG perioperative and myasthenia crisis, these adverse factors will gradually be overcome.

Regardless of the median sternotomy or thoracoscopic thymectomy, we always advocate extended thymectomy for the thymus, that is, complete resection of the thymus tissue, and removal of adipose tissue and ectopic thymus in the cervical root and anterior mediastinum area. We believe that myasthenia gravis is not entirely caused by thymoma. In some cases, hyperplasia of thymus tissue around the tumor may be the real cause of MG, and combined with the presence of ectopic thymic microscopic thymoma, simple thymoma resection, or thymectomy for myasthenia gravis, any of these operations may have adverse effect on treatment, and even induce postoperative myasthenic crisis. The occurrence of MG after single thymectomy has been encountered many times in previous work and has been reported in the medical literature. Therefore, extended thymectomy should be the standard surgical treatment for thymoma, whether it is combined with MG or not. Complete thymoma resection is vital for long-term curative effect in patients with thymoma.

Part IX

Obstetrics-Gynecology and Ophthalmopathy

Acute Pulmonary Embolism After Local Resection of Choroidal Melanoma

37

Weihong Yu

Choroid melanoma is a rare but primary ocular malignancy in adults, with an annual incidence of 6–7 cases per million people. Treatment options include radiotherapy (plaque brachytherapy, proton beam or stereotactic radiotherapy) and laser therapy. Transretinal endoresection using vitrectomy of choroidal tumors is performed only in a few centers because it requires special skills and hypotensive anesthesia, and also because of the concern of tumor seeding.

Beijing Tongren Eye Center reported three cases of life-threatening complication of acute pulmonary embolism (APE) out of 682 cases of uveal melanoma local resection surgery during 1997–2011. All these three APE occurred within hours after surgery. The patients complained of discomfort, chest tightness, chest pain, and gasp with cyanosis. The BP dropped below 90/60 mmHg, and ECG showed sinus tachycardia, lung-shaped P wave, and change in ST-T and SITIII. The blood gas analysis showed lowered PaO_2, elevated $PaCO_2$, and lowered SaO_2. Ultrasonic cardiogram detected right ventricular enlargement. Chest X-ray showed pleural effusion. Two patients died and one patient received thoracentesis, low-molecular-weight heparin, and warfarin for anticoagulant therapy and eventually recovered.

The mechanism of emboli remains unknown. It is speculated that the emboli in these three cases may be derived from lower extremity venous thrombus. The first two patients, who died, received general anesthesia with controlled hypotension. The intraoperative BP was lowered to 75/40 mmHg or 90/50 mmHg. The third patient received local anesthesia, and the BP was maintained normal during surgery. Since none of these two death cases underwent biopsy examination, other embolism sources including tumor tissue and silicone oil droplets could not be ruled out. Hypotensive general anesthesia reduced surgical bleeding, but it could also be a predisposing factor of thrombosis. The third patient received local anesthesia instead of general anesthesia; therefore it is also speculated that local resection surgery could possibly trigger the stress response and lead to embolism.

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_37

Ocular Silicone Oil "The Silk Road"

38

Bo Wan and Rongping Dai

38.1 Introduction

Silicone oil is usually accepted as a commonly effective method for intraocular tamponade in the repair of retinal detachment caused by giant retinal tears, proliferative retinopathy, trauma, or acute retinal necrosis syndrome, and the injection of which could prolong tamponade than gas [1]. Although considered as a safe agent, many side effects of intraocular silicone oil have been reported in literature including band keratopathy, glaucoma, cataract formation, optic atrophy, and reproliferation of membranes beneath the oil interface. Meanwhile, silicone oil may also migrate to subconjunctival space, anterior chamber, subretinal space, and orbit leading to intraocular complications in some cases [2]. Nevertheless, migration of silicone oil through the optic nerve to the brain is rarely described; the mechanism is still not well understood [3, 4].

38.2 Intracranial Migration of Ocular Silicone Oil

The path of silicone oil entering the subarachnoid space and ventricles from the vitreous cavity has been reported by authors, and there are several hypotheses of intraventricular migration, one of which indicates a pseudo-Schnabel cavernous degeneration mechanism [5]: silicone oil may enter the subarachnoid spaces around the optic nerve with a persistent increase of the intraocular pressure, then migrate through the lamina cribrosa into the optic nerve, and eventually reach the ventricular system. Another hypothesis proposes that deep cupping of the optic disk on count of intraocular hypertension may lead to this gradual migration of silicone oil by breaking through the cerebral pia [6]. Anatomic changes such as an optic pit or coloboma may result in the migration too [7]. However, the mechanism still remains to be fully elucidated.

38.3 Imaging Findings

Imaging examinations, such as magnetic resonance image (MRI) and computed tomography (CT), have played a significant role in diagnosing the intracranial migration of intraocular silicone oil [8, 9]. There is a characteristic radiographic appearance on imaging. In head CT examination, a hyperdense globular material can be found in ventricular regions including the frontal or temporal horns, and the signal is similar to intraocular silicone oil with an attenuation values between 70 and 140 Hounsfield units (HU), higher than blood. Meanwhile, brain MRI images can demonstrate that silicone oil is hyperintense on T1-weighted imaging and prominent chemical shift artifact on T2-weighted imaging. The movement of intraventricular silicone oil provides another means to distinguish it from other materials like blood or air on imaging.

38.4 Diagnosis and Treatment

Patients with intracranial migration of intraocular silicone oil always suffer from repeated seizures, headaches, dizziness, or nausea, but some of them are asymptomatic which may easily lead to misdiagnosis [10, 11]. Thus, to integrate clinical presentations with migration of silicone oil is essential. As a rare complication of intraocular endotamponade, intraventricular silicone oil usually associates to the history of surgery and ocular hypertension. Meanwhile, the imaging findings are important for diagnosis and differential diagnosis. In the majority of patients who are asymptomatic, treatment is not needed. It is reported that a patient experienced headache and received ventriculoperitoneal shunt treatment at last [12].

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_38

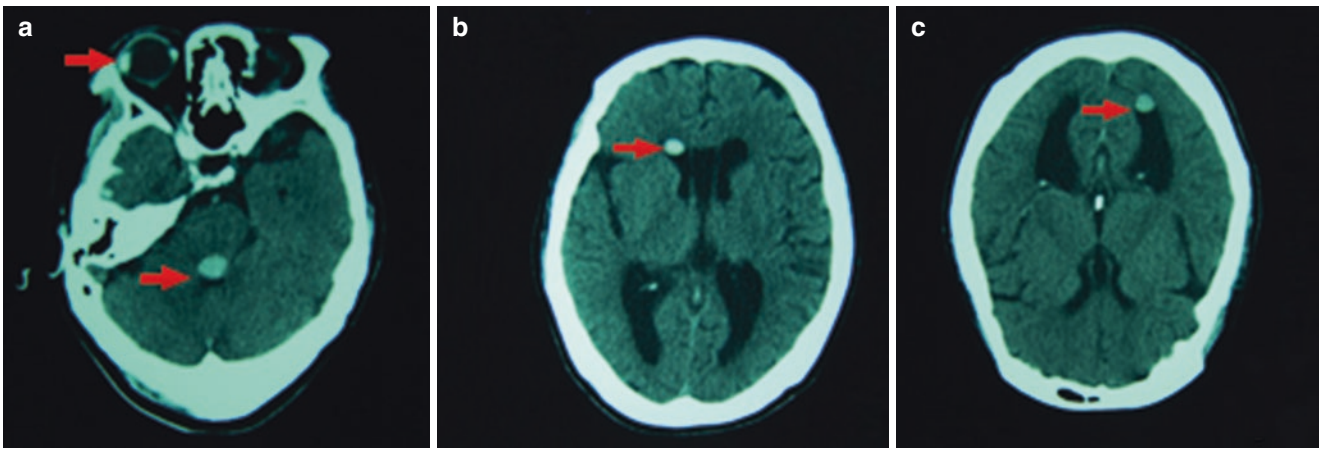

Fig. 38.1 (**a**) Axial non-contrast head computed tomography (CT) reveals high signal intensity of the fourth ventricle (arrows), similar to the characteristics of the intravitreal silicone oil in the right eye (arrow). (**b**) CT scan demonstrates silicone oil (arrow) in the right frontal horn. (**c**) CT shows silicone oil (arrow) migrated to posterior horn as the patient's position changed from supine to prone

We have described a case of 62-year-old woman with tractive retinal detachment caused by proliferative diabetic retinopathy. She experienced poor vision acuity, ocular hypertension, and short-term unconsciousness after pars plana vitrectomy and injection of silicone oil for months. Deep cupping depth of the optic disk was detected. Spherical foreign substances in ventricles shifting with the change of position were found by head CT imaging (Fig. 38.1). According to those characteristics, this patient was eventually diagnosed as intravitreal silicone oil migration into the cerebral ventricles [13].

References

1. Saw SM, Gazzard G, Wagle AM, et al. An evidence-based analysis of surgical interventions for uncomplicated rhegmatogenous retinal detachment. Acta Ophthalmol Scand. 2006;84:606–12.
2. Nazemi PP, Chong LP, Varma R, et al. Migration of intraocular silicone oil into the subconjunctival space and orbit through an Ahmed glaucoma valve. Am J Ophthalmol. 2001;132:929–31.
3. Cosgrove J, Djoukhadar I, Warren D, et al. Migration of intraocular silicone oil into the brain. Pract Neurol. 2013;13:418–9.
4. Fangtian D, Rongping D, Lin Z, et al. Migration of intraocular silicone into the cerebral ventricles. Am J Ophthalmol. 2005;140:156–8.
5. Shields CL, Eagle RC Jr. Pseudo-Schnabel's cavernous degeneration of the optic nerve secondary to intraocular silicone oil. Arch Ophthalmol. 1989;107:714–7.
6. Papp A, Toth J, Kerenyi T, Jackel M, Suveges I. Silicone oil in the subarachnoidal space—a possible route to the brain? Pathol Res Pract. 2004;200:247–52.
7. Eller AW, Friberg TR, Mah F. Migration of silicone oil into the brain: a complication of intraocular silicone oil for retinal tamponade. Am J Ophthalmol. 2000;129:685–8.
8. Williams RL, Beatty RL, Kanal E, et al. MR imaging of intraventricular silicone: case report. Radiology. 1999;212:151–4.
9. Chen JX, Nidecker AE, Aygun N, et al. Intravitreal silicone oil migration into the subarachnoid space and ventricles: a case report and review of literature. Eur J Radiol Extra. 2011;78:e81–3.
10. Campbell G, Milbourne S, Salman UA, et al. Ocular silicone oil in the lateral cerebral ventricle. J Clin Neurosci. 2013;20:1312–3.
11. Chang CC, Chang HS, Toh CH. Intraventricular silicone oil. J Neurosurg. 2013;118:1127–9.
12. Hruby PM, Poley PR, Terp PA, Thorell WE, Margalit E. Headaches secondary to intraventricular silicone oil successfully managed with ventriculoperitoneal shunt. Retin Cases Brief Rep. 2013;7(3):288–90.
13. Fangtian D, Rongping D, Lin Z, Weihong Y. Migration of intraocular silicone into the cerebral ventricles. Am J Ophthalmol. 2005;140:156–8.

39 Eye Diseases Associated with Otorhinolaryngology Head and Neck Surgery

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39.1 Overview

After nose-eye-associated diseases and the related concepts were proposed [1], rhinology-based nose-eye-associated surgical work was rapidly promoted and generalized, which in turn promoted relevant basic and clinical application studies. Similarly, according to the anatomical basis and similar concept, the clinical diagnosis and treatment of ear-, nose-, throat-, and head and neck-associated eye diseases also demonstrate the cooperation of multiple disciplines, including the integration of diagnostic techniques and methods. In recent years, the diagnosis and treatment of such diseases, especially in terms of treatment technique, have benefited from the generalization and development of endoscopic surgery techniques. Clinically, the most representative surgeries are transnasal endoscopic surgeries for chronic dacryocystitis, traumatic optic neuropathy, and orbital diseases. In other words, at present, the mainstream of clinical development is the surgical treatment of ear-, nose-, and throat-associated eye diseases with endoscopic technique-led transnasal endoscopic surgery. The combination of the theory and the practice also attracts many ophthalmologists to learn and master endoscopic techniques, which breaks through their traditional fields and results in the popularization and application of new technologies.

Although the domestic clinical practice and application studies (e.g., endoscopic transnasal optic nerve canal decompression and endoscopic transnasal dacryocystorhinostomy) on otorhinolaryngology head and neck surgery-associated diseases were all reported initially in the otorhinolaryngology head and neck surgery fields [2, 3], interdisciplinary cooperation is a particularly important prerequisite for such an interdisciplinary subject that is developed based on an interdisciplinary content.

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39.2 Lacrimal Duct Disease

Chronic dacryocystitis is a common and representative one of nose-eye-associated diseases. In 1904, Toti first performed dacryocystorhinostomy via an external nasal approach. This surgical method has been used for over 100 years and is still popular nowadays. However, since its appearance in 1988, endoscopic technique has changed the methods for the clinical diagnosis and treatment of dacryocystitis [4]. After domestic scholars reported the clinical efficacy and preliminary results of endoscopic transnasal dacryocystorhinostomy in 1994, more surgeons started to learn and practice an endoscopic transnasal approach, which promoted the generalization and development of nose-eye-associated surgeries.

The surgery process of dacryocystorhinostomy fully shows the advantages of endoscopic nasal surgery for rhinologists. However, the puzzling question is why there is still an overflow of tears when the epithelium of the generated canal is good and the wash of the lacrimal duct is unobstructed. To answer this question, we need to understand the physiological process of tear excretion: in the "lacrimal pump mechanism," the siphon effect of the puncta is crucial, while the normal bones and muscles around the lacrimal duct also play supportive roles for the lacrimal sac. Therefore, when the structure of the puncta is damaged due to multiple probing operations, the siphon effect will be destroyed, which will directly affect the tear excretion function of the lacrimal duct. If the pore of dacryocystorhinostomy is too large and too high, the supportive roles of the bones and muscles to the lacrimal sac will be reduced, and the effect of lacrimal pump will also be weakened, which will result in difficulty in tear excretion. Therefore, some scholars have suggested that dacryocystorhinostomy should be performed at a lower position [5]. However, Wang et al. [6] suggested that if dacryocystitis was recurrent, if the patient had undergone lacrimal duct laser surgery, or the obstruction position of the nasolacrimal duct was high, then a higher position of the lacrimal sac pore was needed. In addition, Min Wang also provided relevant

N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_39

evidence for surgical indications. However, in the analysis of the related factors that affect the long-term efficacy of this procedure, some scholars found that the size of the bone window and the formation of granulations or scars during the repair of the exposed bone surface were risk factors for stenosis or atresia of the generated canal [7, 8]. Therefore, rhinologists started to explore methods to retain the mucosa to improve the surgery's efficacy. When making an incision in the nasal cavity and on the dacryocyst inner wall, pedicle valves were made in both cases to cover the exposed bone surface or wound. After the lacrimal sac valve and nasal mucosa were matched, granulation and scar formation could be inhibited or reduced, which would improve the efficacy of dacryocystorhinostomy [9–11]. At present, the use of a mucosal flap in the nasal cavity and lacrimal sac has become a standard component of dacryocystorhinostomy. As mentioned above, hole-making was only one step of the treatment; the recovery of lacrimal duct function required the surgeon to fully understand the "lacrimal pump mechanism" so that the surgical efficacy could be objectively evaluated before and after the procedure. Since the popularization of transnasal dacryocystorhinostomy, rhinologists have also mastered techniques of lacrimal passage probing or lacrimal duct cleaning. However, because patients frequently visit eye clinics, rhinologists have a limited opportunity for the clinical practice of eye-related procedures; therefore, the main advantage of rhinology is still reflected in the simultaneous treatment of nasal lesions. Therefore, upon the advent of new technologies, interdisciplinary integration and mutual learning are particularly important, as they can effectively promote the further development of new technologies.

39.3 Orbital Disease

Ultrasonic testing is a common physical examination in ophthalmology, though rhinologists know little about it. Ultrasonic testing has a very good reference value in the diagnosis of orbital diseases, particularly in the identification of cystic, solid, or mixed space-occupying lesions. Doppler ultrasound is very helpful in the diagnosis of orbital vascular space-occupying lesions and vascular malformation lesions.

In terms of the treatment of transnasal orbital diseases, the common treatment is for blowout orbital fractures and orbital tumors. Rhinologists seem to be more focused on the endoscopic technique itself because of the greater advantages of endoscopic orbital wall reconstruction. However, ophthalmologists are also concerned with the recovery of visual function (such as the presence or absence of diplopia and visual acuity) and the recovery of facial appearance (such as the presence or absence of eye retraction) while restoring the orbital integrity.

Transnasal orbital surgery takes full advantage of the anatomical structural relationship between the orbit and the nose. After the ethmoid sinus is open through the nasal cavity, a more convenient access to the orbit is formed. The orbital wall, papyracea, and periosteum are very thin; after they are open, the orbit is accessible. However, the largest difference between the sinus and the orbit is that the former has a solid (bony) body cavity, while the latter is a solid organ filled with soft tissue. The bony body cavity gives the surgeon an operable space, and the operation is less susceptible to the surrounding tissue; however, the orbit is different. Because the orbital contents are a group of organs, all of which have important functions, the surgeon cannot create operative space through "partial resection." Second, during the surgery, attention should be paid to the protection of the optical nerve, especially for patients with better preoperative vision and without eye movement disorders.

Endoscopic resection of cavernous hemangiomas at the orbital apex region is a representative surgery of the transnasal resection of orbital tumors. Due to the tumor's deep location and the longer path required to expose the tumor, eye surgery employing a traditional external approach may cause new dysfunction, and the exposure of the surgical field is limited, while transnasal endoscopic resection of cavernous hemangiomas at the orbital apex region satisfactorily solves the above issues. To reduce the operational difficulties after entering the orbit, ophthalmologists may choose to sever the medial rectus muscle at first after the tumor is sufficiently exposed and removed, at which point the medial rectus muscle is reset and sutured so that it does not affect the motor function of the eyeball [12], while rhinologists try to use medical cotton slices to push the orbital fat and orbital muscle so that they can enter the orbit to facilitate the exposure and removal of the tumor. After the surgery is completed, the perpendicular plate ethmoid bone is used to rebuild the orbital wall [13]. Some rhinologists use a thread to pull the ipsilateral medial rectus muscle from the contralateral posterior nostril or nasal septum to expose the tumor for the procedure [14]. All of these strategies reflect the respective strengths of rhinology and ophthalmology and the obvious disciplinary characteristics in different surgical procedures.

39.4 Optic Neuropathy

The objective examinations of traumatic or nontraumatic optic neuropathy include visual evoked potentials and fundus images (including fluorescein angiography). We once tried to identify an objective preoperative evaluation means, but we failed to discover characteristic changes in the fundus of traumatic optic neuropathy; in contrast, nontraumatic optic neuropathy was mostly a chronic progression process, and the fundus showed signs of optic atrophy. In comparison,

fundus images are of great significance for the diagnosis of central artery occlusion in the fundus. Therefore, an objective evaluation method that is associated with surgical efficacy and prognosis is essential for optic neuropathy resulting from a variety of causes.

Optical coherence tomography (OCT) is a new noninvasive technique that can rapidly display cross-sectional images of retina and other ocular structures. OCT can measure the thickness of the retinal nerve fiber layer and can record the axon loss of ganglion cells resulting from any optic neuropathy. At present, OCT is mainly used in the diagnosis of macular disease. If a rhinologist is familiar with the OCT, a more ideal method that can evaluate optic neuropathy may be found.

A more traditional surgical method for traumatic optic neuropathy is the external nasal approach that is completed by the cooperation of ophthalmologists and rhinologists, but endoscopic technology has changed this mode of operation. Except for skull base fracture complications, it has become a consensus that a transnasal endoscopic optic canal decompression open surgery should be performed as soon as possible, and a hormone- and microcirculation-improving drug-based drug therapy should be considered before and after the procedure. After the entire optic canal is decompressed, it is still controversial whether the sheath needs to be cut open; therefore, a strict clinical control study is required to provide evidence.

Optic canal decompression for nontraumatic optic neuropathy is mostly associated with tumor lesions, and the surgery has a certain degree of difficulty. Ossifying fibroma and bone fibrous dysplasia are the typical cases, though some other benign and malignant tumors can originate from the orbit or the sinus and the skull base. Because their main manifestations include decreased vision or exophthalmos, the patients often visit the eye clinic first; however, these diseases are caused by various nasal and skull base lesions. From a technical point of view, it is feasible to perform a transnasal lesion resection (which can be guided by image navigation technology) and optic canal decompression; however, the crux of the issue is how to determine the surgical indications. Currently, the more widely recognized indications for surgery include obvious vision loss, related headaches, exophthalmos, and other conditions that affect the patient's appearance. The controversy involves the following: if the patient has the above symptoms only on one side while the contralateral side is normal, when the lesion is surgically removed, does optic canal decompression need to be performed for both sides at the same time? Surgeons with different levels of experience provide different answers. Even surgeons who are more skillful in endoscopic techniques also experience a process of overcoming the learning curve in the surgical treatment of this disease. In determining the surgical indications, the most important is the evaluation of ophthalmology-related functions.

In the description of the diagnosis and treatment of the above three typical otorhinolaryngology head and neck surgery-related eye diseases, we discussed the important significance of mutual learning and cooperation between otorhinolaryngology head and neck surgery and ophthalmology in the diagnosis and treatment of these diseases. In terms of examination, the interpretation of special examination results can particularly reflect the specialty characteristics. A proper understanding of ophthalmic examination can not only help the surgeon to determine the surgical indications but can also help in the assessment of the surgical efficacy. In terms of treatment, at present, rhinology plays a leading role in the endoscopic technology-based nose-eye-related surgery, which is mainly reflected in its strength in surgical procedures. Ophthalmology focuses itself on the pre- and postoperative systematic evaluation of a patient's visual functions and the intraoperative handling of the orbital content. Of course, otorhinolaryngology head and neck surgery surgeons have also begun to learn relevant knowledge of ophthalmology and to pay attention to the impacts of disease and treatment methods on orbital functions in the course of treatment. In the future, the understanding of the technical contents will be broader, and the surgeon's proficiencies in anatomy and endoscopic operation will no longer be the primary factors that restrict the development of the discipline. Only when the coordinated development of disciplines is emphasized to integrate the different advantages of different disciplines can the treatment of otorhinolaryngology head and neck surgery-related eye diseases experience the greatest improvements.

References

1. Bu GX. Surgical relationships between the nose and the eye. Beijing: People's Medical Publishing House; 1995.
2. Zhou B, Tang X. Endoscopic transnasal dacryocystorhinostomy: results in 35 cases. Chin Arch Otolaryngol Head Neck Surg. 1994;1(2):80–3. https://doi.org/10.16066/j.1672-7002.1994.02.005.
3. Shi JB, Xu G, Li Y. Research of optic canal decompression by transnasal endoscopic approach. Chin J Otorhinolaryngol. 1998;33(4):225–7. https://doi.org/10.3760/j.issn:1673-0860.1998.04.011.
4. Tatlisumak E, Aslan A, Cömert A, et al. Surgical anatomy of the nasolacrimal duct on the lateral nasal wall as revealed by serial dissections. Anat Sci Int. 2010;85(1):8–12. https://doi.org/10.1007/s12565-009-0044-z.
5. Yung MW, Hardman-Lea S, et al. Endoscopic inferior dacryocystorhinostomy. Clin Otolaryngol Allied Sci. 1998;23(2):152–7.
6. Wang M, Wang SQ, Zhang J, et al. Rosenmüller valve during endoscopic dacryocystorhinostomy in treating refractory nasolacrimal duct obstruction. Chin J Otorhinolaryngol Head Neck Surg. 2016;51(7):522–7. https://doi.org/10.3760/cma.j.issn.1673-0860.2016.07.008.
7. Zhou B, Han DM, Huang Q, et al. Long-term follow-up for outcomes of intranasal endoscopic dacryocystorhinostomy. Chin J Otorhinolaryngol Head Neck Surg. 2008;43(1):13–7.
8. Ali MJ, Psaltis AJ, Bassiouni A, et al. Long-term outcomes in primary powered endoscopic dacryocystorhinostomy. Br J

Ophthalmol. 2014;98(12):1678–80. https://doi.org/10.1136/bjophthalmol-2014-305510.
9. Wormald PJ. Powered endoscopic dacryocystorhinostomy. Laryngoscope. 2002;112(1):69–72. https://doi.org/10.1097/00005537-200201000-00013.
10. Massegur H, Trias E, Ademà JM. Endoscopic dacryocystorhinostomy: modified technique. Otolaryngol Head Neck Surg. 2004;130(1):39–46. https://doi.org/10.1016/j.otohns.2003.08.011.
11. Zhou B, Huang Q, Han DM, et al. Modified intranasal endoscopic dacryocystorhinostomy. Chin Arch Otolaryngol Head Neck Surg. 2008;15(2):87–91. https://doi.org/10.16066/j.1672-7002.2008.02.012.
12. Wu W, Selva D, Jiang F, et al. Endoscopic transethmoidal approach with or without medial rectus detachment for orbital apical cavernous hemangiomas. Am J Ophthalmol. 2013;156(3):593–9. https://doi.org/10.1016/j.ajo.2013.05.001.
13. Zhang N, Huang Q, Zhou B, et al. Transnasal endoscopic removal of orbital apex cavernous hemangioma. Chin J Otorhinolaryngol Head Neck Surg. 2013;48(3):204–8. https://doi.org/10.3760/cma.j.issn.1673-0860.2013.03.007.
14. Tomazic PV, Stammberger H, Habermann W, et al. Intraoperative medialization of medial rectus muscle as a new endoscopic technique for approaching intraconal lesions. Am J Rhinol Allergy. 2011;25(5):363–7.

Pregnancy-Related Retinopathy

40

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40.1 Introduction

Gestation period is a time span from fertilization to giving birth to a baby for women of childbearing age, a process both for a fetus absorbing its maternal nutrition and for the maternal body having adaptive changes. During pregnancy, the maternal body would have systemic, temporary, high-load, metabolic stress reaction in all systems, organs, tissues, and cells under the hormone changes; in these particular situations the systemic arterial blood vessels can take change, which would manifest and even lead to disease in all systems of the whole body, while the retina with microvessels is very sensitive to the changes mentioned above. During pregnancy, the probability of gestational hypertension disorders complicating with retinal vascular disease and central serous chorioretinopathy is significantly increased. For this special group, ophthalmology doctors and obstetricians often face tough decisions such as whether to perform active treatment for the primary disease or not, whether it is necessary to take active eye care or not, and whether to give up the treatment or even recommend termination of pregnancy or not. From the HIM thought, we realize that complications during pregnancy period are based on the special physiological changes of this period and time-limited; for example, when the retinal artery spasm has only functional damage and has not been formed for the organic change, it might regress spontaneously during the postpartum period; on the other hand, pregnancy includes dynamic changes, and the severity of retinal vascular lesions and damage will reflect the seriousness of the other organ damage in the whole body, which should be actively intervened. Therefore, the holistic concept should be established, and with a comprehensive understanding of the natural course of fundus lesions during pregnancy, the whole body could be analyzed in a cross-organ level, associated with obstetrical department, and thus the crises would be prevented before they occur.

Having the hormones produced in the placenta involved and influenced by the neuroendocrine system, the cardiovascular, blood, immunity, metabolism, and so on of pregnant women would have changed during pregnancy. Those series of physiological changes are to meet the needs of the fetal growth and development, and to prepare for delivery. Visual system will also change, especially during the second and third trimesters of pregnancy, when the level of estrogen is significantly higher and the moisture content of collagen increases, and thus the local anatomy of the eye, corneal sensitivity, intraocular pressure, etc. will change in this stage, manifested with symptoms as ptosis, pigmentation surrounding the eye, corneal edema, vision loss, and constriction of visual field, which are mostly restored within a few weeks to 2 months after delivery. Concomitant diseases during pregnancy, such as hypertensive disorder complicating pregnancy, diabetes, hyperthyroidism, and childbearing damage to eyes, can make the dysfunction of the visual system and cause or aggravate the ocular retinopathy; although most of the eye diseases are transient, permanent visual impairment could still be possible, which should be paid attention to by clinical doctors.

40.2 Retinopathy in Hypertensive Disorder Complicating Pregnancy

Hypertensive disorder complicating pregnancy (HDP) is a common disease of obstetrics, which usually occurs after 20 weeks of pregnancy, with clinical features such as high blood pressure, proteinuria, edema, and convulsions or coma in severe cases, which is life-threatening for both mother and fetus. As reported in literature, the incidence rate in China is

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N. Wang (ed.), *Integrative Ophthalmology*, Advances in Visual Science and Eye Diseases 3,
https://doi.org/10.1007/978-981-13-7896-6_40

9.4–10.4% [1] and 7–12% [2] abroad. It could be mainly divided into five types: gestational hypertension, light and severe preeclampsia, eclampsia, chronic hypertension complicated with preeclampsia, and pregnancy with chronic hypertension. Among them, the HELLP syndrome belongs to severe pregnancy complications characterized as hemolysis (H), elevated liver enzyme (EL), and low platelets (LP), and the incidence of preeclampsia and eclampsia was 4–16% [3]. HDP is a multiple system disease of unknown causes, with pathogenesis including genetic predisposition, placental ischemia, immune imbalance, oxidative stress, endothelial injury, and so on, which has the final common pathway as endothelial collagen exposure, platelet activation, and PGI_2/TXA_2 change. The basic pathological changes are spasm of systemic arterioles and loss of blood perfusion in the organs of each system, and the resulting retinopathy is well known as an ophthalmic complication during pregnancy.

40.2.1 The Incidence of Eye Diseases Complicating with HDP

HDP can involve conjunctiva, choroid, optic nerve, and visual cortex, while it is most commonly seen that the retina and its blood vessels are involved. According to the literature [4], the incidence of HDP complicating with fundus changes was 53–86%, the spasm and stenosis of retinal arterioles can reach to 36–67.3%, and retinopathy accounts for 6.5–29.7%. With the progression of the disease, the incidence of fundus changes in preeclampsia-eclampsia can be as high as 100% and the incidence of retinal detachment is 2% [5]. The visual function of the patient can be affected, and 40% of the patients can have visual impairment. Other ocular symptoms include amaurosis, visual hallucination, blind spot, diplopia, color anomalopia, and homonymous hemianopsia [6].

40.2.2 Pathological Changes and Mechanisms of Occurrence

A research [7] has found that the retinal and choroid vessels have different regulatory mechanisms. The local blood circulation of the retina is not controlled by the sympathetic nerve, but is mainly relied on self-regulation. When blood pressure rises sharply, it will stimulate normal retinal blood vessels, and the vascular tension would be increased through the autonomic regulation mechanism, yet if the blood pressure keeps on rising, the regulating mechanism will fail, thus leading to the expansion of terminal capillaries and blood-retinal barrier damage, causing retinal ischemia, hemorrhage, cotton-wool spots, and edema, eventually hardening of the arteries. Tension of choroid blood vessel is mainly managed by the sympathetic nervous regulation, and circulation of high blood pressure reactivity can cause reactive contraction of choroid arterioles; if the blood pressure is beyond the limitation of the sympathetic nervous regulation ability, it will destroy the choroid vascular bed, resulting in obstruction and ischemia in choroid, and ischemia in retinal pigment epithelium (RPE) and outer retina, exudative retinal detachment, and long-term pigment change.

40.2.3 Clinical Manifestations

40.2.3.1 Changes in Ocular Fundus

The changes in ocular fundus in HDP are divided into three stages: arteriospasm, sclerosis, and retinopathy. Patients with the disease sometimes directly come into the retinopathy stage without the stage of sclerosis [8]. Retinal artery spasm is the earliest and most common manifestation of HDP, which is similar to primary hypertension, but with the degree of stenosis more significant. It may infringe one or several arteries first, and then show periodic spasm or extensive contractions, and the ratio of arterial to venular caliber changes to 1:2 even 1:4 from the normal value as 2:3. With the progress of the disease, the focal spasm of the vessel changes into extensive stenosis, and the blood vessels show organic sclerosis instead of functional shrink, then the reflect light of the fundus arterial wall was enhanced, the caliber narrows down, and the arteriovenous cross-pressure signs are indicated. For the time of duration from spasm stage to sclerosis stage, the [9] reports were inconsistent, most of the cases had stenosis, and sclerosis occurred after 2 weeks, while for some cases it showed up several weeks or months later. Due to the severe spasm and contraction of the arteries, the retinal vascular barrier has been damaged, causing lesions in retina, optic disc retina, and choroid, such as multiple bleeding points, edema, cotton wool spots as exudate, and papilledema. HDP-caused lesions in choroid are characterized as yellow-white focal lesions of retinal pigment epithelium, and for the severe cases there could be serous retinal detachment.

Serous retinal detachment is generally considered to be specific to preeclampsia-eclampsia; as diastolic blood pressure is >120 mmHg and proteinuria is +++, we should be alert to serous retinal detachment combined with papilledema. Early literatures [10] reported that the incidences of serous retinal detachment occurring in preeclampsia and eclampsia were, respectively, 1% and 10%, and more recent studies have shown that the incidence rises to 32% and 65%, which could be related to the improvement of inspection equipment and diagnostic level. The pregnant women have less activity, whose blood stream is slow, with physiological hypercoagulation, arteriolar spasm of HDP, and endothelial damage as the basic pathological changes. They are high-risk groups for thrombosis, and there might be complications like placental abruption or stillbirth. At the same time, a large

amount of coagulant substances were released into the bloodstream, activating exogenous coagulation system and inducing acute disseminated intravascular coagulation (DIC). As a result, vascular occlusion in retina and choroid might appear, resulting in RPE ischemia, dysfunction, secondary retinal detachment in macular area and optic disc. Cunningham reported [11] that the reason of patients with preeclampsia getting multiple retinal artery occlusions also relates to the rare high coagulation state of protein S deficiency apart from the above risk factors. Retinal detachment is usually bilateral, spherical, and located at the inferior retina, and the exudate may come from the retina and choroid, or separately from the choroid blood vessels. Research [12] has proved with venography that, retinal detachment may be due to the choroid blood vessel pressure, and then the accumulation of fluid leakage from subretinal space, which is caused by injury of retinal pigment epithelial cell, would result in detachment of retina.

40.2.3.2 Changes in the Visual Function

Blurred vision, amaurosis, visual hallucination, and diplopia are the primary symptoms in choroid retinal and pathological changes with HDP. When the fundus changes in spasm stage, patients would be with only mild blurred vision, which is easy to ignore in clinical practice, while most patients have got retinal dema, exudate, or splinter hemorrhage, and even limited retinal detachment when the visual blur is apparent. And when the visual deformity indicated the edema and seepage of macular area, it usually means that the lesions had entered into the third stage. For the apparently detached retina, there can be felt as being covered by a fixed black shadow. In severe cases, the visual acuity drops to only a light perception. This may be accompanied by papilledema and irreversible damage to optic nerve. After the reposition of retina, about 50% of patients have optic nerve atrophy or macular pigment disorder, and even lose light perception. The loss of vision and changes of fundus caused by this mostly subsided within weeks of postpartum, and then the vision returned to normal [13].

The visual impairment caused by HDP is mainly related to the fundus lesion, but a very few cases are caused by the involvement of the cerebral cortex or the combination of other lesions. It has been reported [14] that for the patients with HELLP syndrome, the traumatic palsy of the sixth pair of cranial nerve leads to transient diplopia, and no other pathological changes were found by brain scan and angiography, and thus it was assured that the diplopia was caused by the strong spasm of vessels supplying the abducens. Visual dysfunction can be caused by various secondary pathological changes in the occipital posterior cerebral artery, vasospasm, or brain edema, and even cerebral ischemia and hypoxia, e.g., loss of vision with normal fundus and pupillary reflex, and disappeared optokinetic nystagmus suggests cortical dysfunction and cortical blindness. Even if the patient lost sense of light, the visual acuity would usually recover within a few days to weeks. MRI is the best imaging examination technique for patients with brain lesions, as its detection of white matter lesions is more sensitive than CT, and MRI on patients with cortical blindness shows enhanced occipital lobe signal. It is reported [15] that the loss of cortical vision in patients with HELLP syndrome is also related to the formation of intracranial vein sinus thrombosis. Therefore, for the pregnant patients with vision loss and normal fundus, it is necessary to consider the cortical blindness and hysteria caused by intracranial venous thrombosis, antiphospholipid syndrome, hemorrhea, etc.

40.2.4 Diagnosis

The retinopathy of HDP patients mainly depended on the increase of blood pressure during pregnancy, the history of vision changes, and the diagnosis and staging in combination with the fundus examination. Bedside direct or indirect fundoscopy is simple, convenient and effective. However, due to the confined magnification of funduscopy examination, the limitations of bedside examination and the subjective factors of inspectors, etc., as well as some limited retinal detachment being not easy to find, thus the reported incidence of HDP patients with retinal detachment varied. As the light stimulation can induce eclampsia, if retinal detachment was taken into consideration, indirect ophthalmoscopy or other noninvasive examinations such as electrophysiological examination on retina should be performed [16]. These checks can be used to identify the retina diseases and other diseases which cause insomnia, such as occipital infarction, vascular spasm, optic nerve ischemia, papilloretinitis, central retinal artery occlusion, or allergy. Optical coherent tomography (OCT) is a noninvasive, simple examination with high resolution and high speed, which can be carried out on the retina at the anatomical level, to quantify the severity of pathogenetic condition, and is suitable for inspection in all layers of retina and choroid capillary layer, as well as a gold standard for determination on retinal histological changes [17]. B-ultrasonography of the eye can also be used for the diagnosis of retinal detachment and curative effect observation. It is economical, simple, and fast, while it can only reflect the changes in the anatomical structure of retina, and it is not helpful for the judgment of retinal function. Fundus fluorescein angiography (FA) and indocyanine green angiography (ICGA) facilitate the diagnosis on retinopathy, which would show that there are retinal artery stenosis, blood capillary leakage, and tissue staining, and no retinal capillary perfusion in cotton wood spot area, and for patients with retinal detachment there should be mottled fluorescein leakage, with staining on subretinal and peripapillary area. Fluorescein

can go through the placenta, and fluorescein and indocyanine green are labeled by the Food and Drug Administration as Category C in Pregnancy and Lactation Labeling Rule, and currently it lacks the definitive epidemiological data to confirm the safety of using this angiography during pregnancy, and thus the method is limited in application, and is only used for the examination for treatment plans, decision-making, etc., which can change the threat of vision depending on the results, and also the informed consent of patients must be obtained [18].

40.2.5 Management Principle

Preeclampsia and eclampsia with HDP are dangerous to the life safety of mother and fetus with unclear pathogenesis, while most scholars believe that it may be closely related to intrauterine content, and thus termination of gestation is the only way to remove the cause, to control the condition, and to improve the prognosis of both mother and fetus. With regard to the time of termination of pregnancy, individualized treatment can be given according to the gestational age, whether there are complications or not, therapeutic effects, and fetal intrauterine conditions. After proper drug treatment, a selective period or timely termination of pregnancy would make patients' systemic symptoms with preeclampsia soon subside. Although ocular symptoms are commonly seen in preeclampsia-eclampsia, most of the retinopathies caused by it are improved after childbirth. According to research data [19] postpartum fundus which restored to normal accounted for 86.8%. Therefore, special treatment is generally not required for the ocular presentation of patients with HDP. The retinochoroid should be examined by ophthalmoscope or fundus photography, OCT, or B-scan ophthalmic ultrasound in patients with HDP, regardless of whether their visual acuity changed or not. Patients with chronic hypertension should be given fundus photography in the early stage for later dynamic observation. As observed on the fundus lesions, the spasm or contraction of retinal arteries falls within functional changes, which could be temporarily reversible. Before the change of diffuse retinopathy or exudative retinal detachment, the illness can be relieved or disappeared by taking measures such as resting, sedation, relieving spasm, and antihypertension, and thus pregnancy can keep going on while the blood pressure and fundus status must be continuously monitored. The retinal artery is the only arteriole that can be directly observed in the whole body, and can indirectly reflect systemic vascular diseases. In the observation for treatment, if progressive decline in vision occurs, fundus examination would show aggravating retinal artery lesions, and retinal edema, exudation, hemorrhage, and detachment, which indicates organic injuries of systemic arterioles, by then, to avoid permanent damage to patients' eyesight; obstetricians might consider timely termination of pregnancy to alleviate the systemic condition and improve both maternal and fetal outcome.

40.3 Other Pregnancy-Associated Retinal Diseases

Previously existing eye diseases include central serous chorioretinopathy, vascular occlusive diseases, myopia, diabetic retinopathy, and exophthalmic goiter. The latter two will be described in other relevant sections.

40.3.1 Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC) is caused by accumulation of choroidal capillary exudate on the space between the retina and pigment epithelium, with secondary retinal detachment, resulting in decreased visual acuity, deformation, and other symptoms. The age of onset is 20–50 years old, and male-to-female ratio is 8:1, and pregnancy is a risk factor of CSC. At present, the CSC during pregnancy is poorly understood, it is not yet clear that whether the performance is coincidental with pregnancy or an independent disease caused by hormonal hypercoagulation during pregnancy or hemodynamic changes. Researchers [20] believe that CSC is different from retinal detachment caused by preeclampsia-eclampsia, as CSC is often unilateral, with no history of other eye diseases other than refractive error, and no history of HDP. It will not develop in most patients until the late trimester of pregnancy and will recover spontaneously several months after birth.

40.3.2 Vascular Occlusion Diseases

With increased level and activity of coagulation factor in gestational period, decreased amount of exercise during periods of pregnancy and childbirth, and slow blood flow of vascular bed, maternal population are all risk factors for thrombosis. A study of cerebrovascular accidents during pregnancy revealed that the risk of cerebral infarction during pregnancy was 13 times higher than that of non-pregnant women, and thus the risk of retinal and choroidal occlusion increases along with it, while retinal-related vein occlusion rarely occurs. It has been reported [21] that there were no other risk factors for unilateral or bilateral cases of central retinal artery occlusion. Visual deterioration, retinal ischemia found in the fundus, stenosis of arterioles, pale optic disc, and visual field defect consistent

with the occlusion area all occurred in the third trimester of pregnancy. It is believed that the retinal artery occlusion may be caused by complement-mediated white thrombus.

40.3.3 Myopia

Myopia is the most common disease endangering health of vision, especially high myopia, for it is prone to be with fundus pathological changes such as macular degeneration, glaucoma, retinal edema, hemorrhage, and even retinal detachment in severe cases. Researchers [22] regarded physiological change in the cardiovascular system of pregnant women as reasons for aggravating chorioretinal angiogenesis of high myopia, and when postpartum blood flow of uterine reduces and the blood volume for circulation in the eye increases, it could damage the neovascularization in fundus. Domestic scholars had studied the changes of fundus before and after delivery in pregnant women with high myopia [22], and it showed that 35 cases of pregnant women during pregnancy had not got any other fundus changes nor other complications; among 11 cases of vaginal delivery, the incidence of fundus changes was 64%, 18% of which was retinal detachment; for the 7 cases of vaginal midwifery recipients, cases with fundus changes accounted for 7 (43%); and there was 29% with fundus changes of the 17 cases of cesarean sections. As the latter two methods of delivery had got not even one case of retinal detachment, it was indicated that the vaginal midwifery and cesarean section might prevent exacerbation of fundus lesions. It could be concluded that, due to the maternal repeated intense effort during delivery, abdominal pressure and peripheral vascular resistance increase and cause excessive extrusion on the eyeball from the ocular muscle, further prompt pathological changes such as vasospastic hemorrhage on the fundus, retinal hemorrhage, and edema, or even retinal detachment. Nonetheless, some scholars [23] did not believe that the stress of pregnancy and childbirth can increase the risk of high myopic retinal detachment, as 50 pregnant women with high myopia had fundus examination in late pregnancy, and no significant changes were found as compared with the vaginal delivery group; in addition, in 10 asymptomatic pregnant women who had pathological changes as high myopia, retinal detachment, and lattice degeneration of retina, after 19 times of natural delivery given by all of gravidas, no new retinopathy was found by the fundus examination. It is believed that the increase in intraocular pressure caused by forced breath holding is evenly distributed within the eyeball, and the vitreous body would not be pulled in a certain direction resulting in retinal detachment or rupture. In view of the increasingly tense situation in the current domestic medical environment and doctor-patient relationship, most of the obstetric institutions are very cautious on choosing the mode of delivery for pregnant women with high myopia. They often use forceps or vacuum extraction to facilitate the delivery, in order to reduce the risk of rhegmatogenous retinal detachment.

References

1. Yang W, Xiaohong T. Prognostic features and influencing factors of hypertensive disorders in pregnancy. Progr Obstet Gynecol. 2013;22(8):666–7.
2. Callaway LK, David MH, Williams GM, et al. Diagnosis and treatment of hypertension 21 years after a hypertensive disorder of pregnancy. Aust N Z J Obstet Gynaecol. 2011;51(5):437–40.
3. Zhenchun Z, Huixia W. Evidence-based progress in diagnosis and treatment of HELLP syndrome. J Pract Obstet Gynecol. 2010;26(4):257–9.
4. Wenzhi M, Liren J. Fundus observation of pregnancy-induced hypertension syndrome. Chin J Pract Ophthalmol. 1998;6(4):278.
5. Omoti AE, Waziri-Erameh JM, Okeigbemen VW. A review of the changes in the ophthalmic and visual system in pregnancy. Afr J Report Health. 2008;12(3):185–96.
6. Wanzhe J, Hui W. Hypertensive disorders and retinopathy during pregnancy. Clin Med. 2010;30(12):84–5.
7. Fengming L. Chinese ophthalmology. 2nd ed. Beijing: People's Medical Publishing House Co., Ltd.; 2005. p. 2154–5.
8. Zhenyu Z, Yingqi L. Fundus change of pregnancy-induced hypertension syndrome and suggestions for new grading method. Chin J Pract Ophthalmol. 1987;5:218–20.
9. Lara-Torre E, Lee MS, Wolf MA, et al. Bilateral retinal occlusion progressing to long-lasting blindness in severe pre-eclampsia. Obstet Gynecol. 2002;100:940–2.
10. Saito Y, Tano Y. Retinal pigment epithelial lesions associated with choroidal ischemia in pre-eclampsia. Retina. 1998;18(2):102–8.
11. Cunningham FG, Fernandez CO, Hemandez C. Blindness associated with preeclampsia and eclampsia. Am J Obstet Gynecol. 1995;172:1291–8.
12. Hayreh SS, Servais GE, Virdi PS. Fundus lesions in malignant hypertension. VI. Hypertensive choroidopathy. Ophthalmology. 1986;93(11):1383–400.
13. Binjiang L, Xiaodong L, Lan L, et al. Clinical analysis of the fundus changes of 350 cases with pregnancy induced hypertension syndrome. Int Eye Sci. 2010;10(12):2356–60.
14. Barry-Kinsella C, Milner M, Mccarthy N, et al. Sixth nerve palsy: an unusual manifestation of pre-eclampsia. Obstet Gynecol. 1994;83:849–51.
15. Beeson JH, Duda EE. Computed axial tomography scan demonstration of cerebral edemia in pre-eclampsia preceded by blindness. Obstet Gynecol. 1982;60:529–32.
16. Zhimin H, Shuhong Z, Guiying B. Clinical study of eye electrophysiology of preeclampsia. J Qiqihar Med Coll. 2006;27(6):670.
17. Somfai GM, Mihaltz K, Tulassay E, et al. Diagnosis of serous neuroretinal detachments of the macula in severe preeclamptic patients with optical coherence tomography. Hypertens Pregnancy. 2006;25(1):11–20.
18. Fineman MS, Maguuire JI, Fineman SW, et al. Safety of indocyanine green angiography during pregnancy: a survey of the retina, macula and vitreous societies. Arch Ophthalmol. 2001;119:353–5.
19. Patel N, Riordan-Eva P, Chong V. Persistent visual loss after retinochoroidal infarction in pregnancy-induced hypertension and disseminated intravascular coagulation. J Neuroophthalmol. 2005;25(2):128–30.

20. Cruysberg JR, Deutman AF. Visual disturbances during pregnancy caused by central serous choroidopathy. Br J Ophthalmol. 1982;66:240–1.
21. Blodi BA, Johnson MW, Gass JD, et al. Purtscher's-like retinopathy after child birth. Ophthalmology. 1990;97:1654–9.
22. Yonghong S. Analysis of 35 cases of pregnancy with high myopia. J Guiyang Med Coll. 2001;26(1):88–91.
23. Neri A, Gusbor R, Kremer I, et al. The management of labor in high myopic patients. Eur J Obstet Gynecol Report Biol. 1985;19:277–9.