REVIEW

PATHOGENESIS OF RETINOPATHY OF PREMATURITY: A LITERATURE REVIEW

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Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that affects premature infants, especially those with low birth weight and high oxygen exposure. It is still the leading cause of blindness in children worldwide. The pathophysiological mechanism occurs in two phases: the first known as hyperoxia-induced vascular regression and the second - hypoxia-induced pathological neovascularization. An imbalance of a large number of molecules and cytokines is involved in the development of this disease. The main ones are: vascular endothelial growth factor (VEGF); insulin-like growth factor-1 (IGF-1); Hypoxia-inducible factor-1 alfa (HIF-1α); as well as a large number of proinflammatory mediators. Various factors such as: oxygen fluctuation, nutritional factors, genetic and epigenetic factors have a certain impact on the development and progression of Retinopathy of prematurity. The motive of this literature review is to present the current views and knowledge regarding the pathophysiological mechanisms as well as potential biomarkers for timely recognition of premature infants at high risk for ROP. For this purpose, we approached a data search from two large databases of biomedical literature: Medline and Embase by entering the keywords: retina, retinopathy of prematurity, hypoxia, pathogenesis, neovascularization. From the obtained data, we selected those papers that present the latest knowledge in this field of ophthalmology. Our perspective on ROP is that insights from its pathophysiological and complex cellular mechanisms should, in the future, contribute to the development and implementation of more sensitive biomarkkers for early diagnosis and tretment prognosis, ultimately aiming to improve outcomes in affected children.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ПАТОГЕНЕЗА НА ПРЕМАТУРНАТА РЕТИНОПАТИЈА: ПРЕГЛЕД НА ЛИТЕРАТУРА

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Печатарски права: ©2025 Игор Исјановски, Стефан Пандилов, Емилија Ѓошевска-Даштевска. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираа торигиналниот(ите) автор(и) и изворот.

Конкурентски интереси: Авторот изјавува дека нема конкурентски интереси.

Извадок

Прематурната ретинопатија е вазопрлиферативно заболување на ретината која ги афектира предвремено родените новороденчиња, особено тие со ниска телесна тежина и висока експозиција на кислород. Се уште претставува водечка причина за слепило кај деца во светот. Патофизиолошкиот механизам се одвива во две фази: прва позната како хипероксија индуцирана васкуларна регресија и втора-хипоксија индицирана патолошка неоваскуларизација. Дисбаланс на голем број молекули и цитокини се вклучени во настанувањето на ова заболување. Централно место заземаат: vascular endothelial growth factor (VEGF); insulin-like growth factor-1 (IGF-1); HIF-1α (Hypoxia-inducible factor-1 alfa) како и голем број на проинфламаторни медијатори. Идејата на овој литературен преглед е да ги прикаже моменталните ставови и сознанија кои се познати во врска со патофизиолошките механизми како и потенцијални биомаркери за навремено препознавање на прематурусите со зголемен ризик за РОП. За таа цел пристапивме кон пребарување на податоци од две големи датабази на биомедицинска литература: Medline и Embase со внесување на клучни зборови: ретина, прематурна ретинопатија, хипоксија, патогенеза, неоваскуларизација. Од добиените податоци ги избравме оние трудови кои ги прикажуваат најновите сознанија во ова поле од офталмологијата. Нашите согледувања за РОП се дека сознанијата од нејзините патофизиолошки и сложени клеточни механизми, во иднина, треба да придонесат за развој и имплементација на почувствителни биомаркери за рана дијагноза и прогноза на третманот, со крајна цел да се подобри исходот кај засегнатите деца.

Introduction

Retinopathy of prematurity (ROP) is a retinal vasoproliferative disease that affects premature infants. Despite all efforts in neonatal care centers, ROP remains the leading cause of blindness in childhood[1]. However, the incidence varies from region to region due to the different levels of neonatal care and survival rates of premature infants. High-income countries have a lower rate of ROP-associated blindness compared to middle- and low-income countries. The main reason for this is thought to be better screening and management of the problem[2].

The etiology of the disease is multifactorial. Several risk factors promote its occurrence. Thus, birth weight and gestational age are considered the most influential in the pathogenesis of ROP. The lower the gestational age and birth weight, the higher the risk of developing the disease. In other words, ROP is rare in newborns born after 32 weeks of gestation and weighing more than 1500 g[3]. Another important risk factor for its occurrence is oxygen. Supplementation with oxygen in combination with atmospheric oxygen disrupts the physiological hypoxia of the retina, which results in a delay in the formation of normal blood vessels, retinal ischemia and the formation of new-pathological blood vessels. The duration of oxygen therapy and the increased concentration of O2 significantly increase the risk of developing a severe form of ROP[4]. In addition to these, many other risk factors have been identified in recent decades that have a greater or lesser impact on this condition. Depending on where they originate, they are divided into: maternal factors, prenatal and perinatal factors, demographic factors, comorbidities of infant, nutritional and genetic factors[5].

The disease was first described by ophthalmologist Theodore L. Terry in 1942 as *"retrolental fibroplasia"* due to the formation of a fibrous membrane behind the lens in blind newborns[6]. About a decade later, it was associated with excessive oxygen supplementation in premature infants. This period is known as the "first epidemic" of ROP. About twenty years later, the so-called "second epidemic" of ROP occurred due to the increased survival rate of extremely premature infants, i.e. those born before 28 weeks of gestation and with a birth weight of less than 1000 g. Despite improved oxygen control, these newborns were at increased risk for developing ROP due to their relatively underdeveloped retinal vascular network and longer stay in intensive care. The second epidemic led to the development of screening programs and laser photocoagulation as a treatment for this condition in the 1980s. Since the 1990s, the so-called "third epidemic" occurring in low- and middle-income countries[7]. The reason for this is that in these countries, neonatal care has improved in recent decades, with better survival of premature infants, but they still lack a systematic screening program for ROP and an inability to treat the condition.

Normal development of retinal blood vessels

The fetus in utero is normally in a hypoxic state with a stable partial pressure of oxygen in the arterial

blood vessels of 22-24 mmHg8. This environment allows for the proper development of blood vessels starting from the level of the optic nerve up to the peripheral avascular retina. Physiological hypoxia stimulates the production of vascular endothelial growth factor (VEGF) which promotes the growth of the vascular network. This molecule is strongly regulated by oxygen. It is produced by astrocytes in the still avascular retina in response to hypoxia. In addition to VEGF, other molecules, such as insulin-like growth factor-1 (IGF-1), are also involved in this complex biochemical-embryonic process[9, 10].

The basis of blood vessels is from mesenchymal spindle cells that originate from the optic disc and progress peripherally and forward towards the outer part of the retina. Blood vessels begin to develop intrauterinely at 15 weeks of gestation. The process is called angiogenesis and occurs simultaneously in both the nasal and temporal sectors of the retina. Nasally, vascularization reaches ora serata around 34–36 weeks of gestation, and temporally it occurs between 36–40 weeks[9, 11].

Unlike hypoxia, hyperoxia inhibits the production of VEGF. Thus, premature infants exposed to high oxygen concentrations have reduced production of VEGF, which disrupts normal blood vessel development, resulting in areas of avascular retina. The lower the gestational age of the newborn, the larger these avascular zones are. This condition not only inhibits the development of the vascular network but also causes vasoconstriction and vaso-obliteration of already formed blood vessels, further aggravating the situation[12]. In this way, the retinal tissue is left without adequate oxygen support, which is the basis of the pathophysiological process in ROP.

The aim of this literature review is to present new insights into the pathophysiological mechanism of this retinal disease. That is, to understand all the molecules, cells and signaling pathways that are involved in the pathobiochemical cascade and progression of retinopathy of prematurity. As well as to present possible potential biomarkers that will find clinical application in the early recognition and appropriate management of this condition.

Materials and methods

In the preparation of this literature review, a search was conducted in two large databases of biomedical literature: Medline and Embase. The following keywords were used: retina, retinopathy of prematurity, hypoxia, pathogenesis, and neovascularization. For the analysis, papers published in English between 2003 and 2024, full-text papers, were selected, and abstracts and papers published in other languages were excluded.

Results and discussion

Pathophysiology of ROP

As previously mentioned, the development of retinal blood vessels begins in the fourth month of gestation. Since the process is completed between 34-40 weeks of gestation, premature infants have an incompletely vascularized retinal periphery. That is, the lower the gestational age of

the premature infant, the larger the avascular retinal zone. The disease is based on the processes of hyperoxia, vascular regression, followed by hypoxia and neovascularization, proliferation and traction. The course of the pathological process is continuous and is divided into two phases[12].

The first phase or initial phase is the one in which there is a decrease or cessation of vascular growth and regression of already developed retinal blood vessels. It is induced by hyperoxia in premature infants who are placed in increased O2 concentrations in intensive care units. And a second phase, or proliferation phase, in which abnormal proliferation of blood vessels occurs, a process induced by previous hypoxia in avascular areas of the retina.

Physiologically, the retina in utero develops in a hypoxic environment that stimulates the production of VEGF as an important cytokine in the formation of blood vessels. In premature infants, the process of angiogenesis is not fully completed, and atmospheric oxygen as well as oxygen supplementation in external conditions suppresses the production of VEGF. This leads to the cessation of normal growth of peripheral blood vessels and regression of those already formed. Thus, as the newborn grows, the retina matures without a sufficient number of blood vessels, which makes it hypoxic. At the same time, apoptosis of endothelial cells occurs, a mechanism that is also involved in the pathological process. Fluctuations in oxygen levels lead to the formation of reactive oxygen species (ROS), and due to the insufficiently developed antioxidant defense in premature infants, ROS damage endothelial cells and pericytes. Damaged pericytes gradually die, which disrupts the stability of blood vessels and worsens the overall situation with the vascular network. These processes lead to a systemic inflammatory response and dysregulation of VEGF and IGF-1[13].

As the newborn grows, the metabolic demand of the retina increases, emphasizing relative hypoxia, which leads to the second phase. In this phase, the secondary hypoxia causes increased expression of VEGF in the retinal tissue. On the other hand, the maturation of organs and tissues in the newborn stimulates increased production of IGF-1. It promotes and maintains high levels of VEGF, which results in neovascularization and proliferation of blood vessels at the transition between the vascularized and avascular retina. Thus, pathologically formed blood vessels begin to develop towards the vitreous. Due to the dysfunction of their development, they are susceptible to leakage, which leads to retinal edema and bleeding, together with proliferation towards the vitreous, causing scar tissue formation and retinal traction. In the final stages, traction ablates the retina, leading to irreversible vision loss - blindness[14]. In the second phase, in addition to VEGF and IGF-1, a large number of other pro-inflammatory cytokines are involved, such as: TNF-α (tumour necrosis factor-alpha), IL-1β (interleukin-1 beta), IL-6 (interleukin-6) and others, which stimulate the formation of abnormal blood vessels and progression of the disease[15].

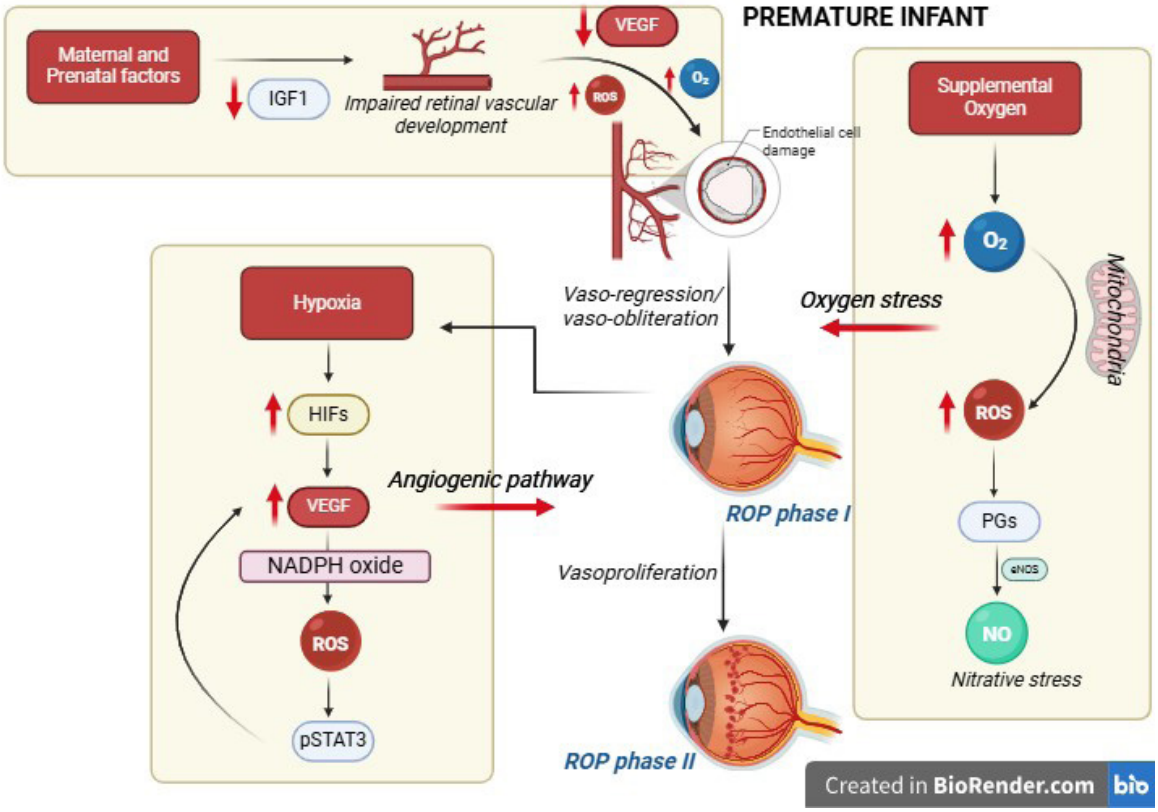


Figure 1: Pathophysiological mechanism and biochemical cascade in retinopathy of prematurity (ROP). IGF1- insulin-like growth factor-1; VEGF-vascular endothelial growth factor; ROS-reactive oxygen species; O_2 – oxygen; PGs-prostaglandines; NO-nitic oxide; eNOS-endothelial NO synthase; HIFs-hypoxia-inducible factors; NADPH-dihydronicotinamide-adenine dinucleotide phosphate; pSTAT3-phophorylated signal transducer and activator of transcription 3.

Stages of ROP

The classification of ROP in terms of the severity of the clinical picture includes 5 stages and 3 zones that describe the level of retinal involvement[16].

Stages I-III have the ability to spontaneously regress at any time, while stages IV and V are most often irreversible and lead to vitreous hemorrhage, tractional retinal detachment and subsequent blindness. The first stage is characterized by the appearance of a white line that demarcates the vascular from the avascular retina. Stage II is specific in that a tissue ridge and small initial neovascular changes appear. With the development of the disease, such initial neovascular blood vessels proliferate through the ridge and towards the vitreous - stage III. Already in stage four, zones of retinal ablation are observed, extrafoveolar (IVa) and intrafoveolar (IVb). In the last, fifth stage, complete retinal detachment occurs. Additional risk factors are designated as “plus disease” and the development of the so-called aggressive ROP, AP-ROP.

Molecular and cellular mechanisms

Role of VEGF and other cytokines in the pathogenesis of ROP VEGF

plays a key role in the physiological but also in the pathological development of retinal blood vessels. As we mentioned earlier, in the first stage of ROP, hyperoxia suppresses the production of VEGF, which leads to a delay in the development of the normal vascular network of the retina. This stimulates the activation of signaling pathways of apoptosis of endothelial cells and the loss of local pericytes, with the ultimate effect of regression of blood vessels. In the second stage of ROP, hypoxia and local acidosis promote the production of HIF-1α (Hypoxia-inducible factor-1 alfa), a major promoter of VEGF. Increased and uncontrolled production of VEGF leads to the formation and proliferation of new blood vessels. HIF-1α also acts on erythropoietin, which also contributes to angiogenesis. It should be emphasized that the angiogenesis mediated in this way is disorganized and uncontrolled. The blood vessels formed by this mechanism are fragile and susceptible to leakage, which leads to retinal edema, hemorrhages, and because they proliferate towards the vitreous, they lead to vitreoretinal traction[17].

Insulin-like growth factor-1 (IGF-1) is a key molecule that affects the function of VEGF. It is involved in the process of normal angiogenesis. In the first phase of ROP, as a result of underdeveloped organ systems in prematurity, the level of IGF-1 is low, therefore preventing the appropriate signaling and action of VEGF. In the second phase of ROP, due to the increased production of IGF-1, it additionally stimulates the production of VEGF, which leads to uncontrolled pathological neovascularization[18.]

As a consequence of the processes of hyperoxia and hypoxia, a pronounced inflammatory response occurs both locally at the retinal level and systemically. The process of hypoxia promotes the activation of microglia cells and macrophages that secrete a large number of pro-inflammatory cytokines: TNF-α, IL-1β, IL-6. Such an inflammatory cascade causes further damage to blood vessels, increases hypoxia in the surrounding tissue, and stimulates neovascularization. The process of fibrosis is also a continuation of this inflammatory event in the retina[15].

Oxidative stress and endothelial damage

Oxidative stress is created in response to a disturbed equilibrium between the production of pro-oxidants and the body's capacity to detoxify them. Most often, these are: free oxygen radicals, nitric oxide (NO), superoxide anions and hydrogen peroxide. In newborns, oxidative stress is particularly pronounced because at birth the newborn passes from an environment with a low to an environment with a higher oxygen concentration. Oxidative stress in the newborn, and especially in premature infants, has a great impact because the mechanisms for antioxidant protection are not yet sufficiently developed. It has been shown through several experimental models that hyperoxia is responsible for increased generation of ROS due to insufficiently developed autoregulatory vascular systems in the retina[19]. On the other hand, hypoxia increases the concentration of oxygen donors and promotes the transfer of electrons to oxygen. It also activates enzymes that generate ROS

in the electron transport system of mitochondria and cause oxygen-induced retinopathy. These two mechanisms of hyperoxia followed by hypoxia are considered key links in the chain of oxidative stress involved in the pathogenesis of ROP[20]. ROS participate in endothelial dysfunction, thereby interfering with the normal development of blood vessels, leading to their regression and obliteration. They damage the blood-retinal barrier by attacking the endothelium and pericytes. The selectivity of this important barrier is lost, making the tissue more susceptible to damage.

Nitro-oxidative stress is another factor considered to be involved in the pathogenesis of ROP. NO reacts with reactive oxygen radicals and generates nitrites, nitrates and peroxynitrites that cause microvascular damage[21].

Lipid peroxidation of cell membranes is also an important oxidative mechanism for endothelial damage to blood vessels and the retina. The retina is highly sensitive to lipid peroxidation because it is made up of lipids with a high percentage of polyunsaturated fatty acids. Nitric stress induces cis-trans isomerization of arachidonic acid, which causes vascular damage to the retina. All of these events lead to a proinflammatory response and the release of many inflammatory mediators, which together are involved in the pathophysiological mechanisms of ROP development[21,212].

The organism tries to cope with oxidative stress through multiple molecules and enzyme systems. Several molecules are considered to play a key role in the antioxidant response of the organism. Ascorbic acid, reduced glutathione, Vitamin E and urate prevent oxidative damage to biological membranes and lipoproteins. They reduce and prevent retinal damage. Omega-3 fatty acids, on the other hand, although through still insufficiently known mechanisms, suppress the inflammatory response, thus having antiangiogenic and neuroprotective effects on the retina. The enzymes: catalase, superoxide dismutase, and glutathione peroxidase play a central role in the antioxidant activity of the body, and are considered an important defense factor against oxidative stress [20].

Influence of other factors in the pathogenesis of ROP

Effect of oxygen therapy and oxygen fluctuation

Oxygen fluctuation causes increased production of ROS that cause endothelial damage. Oxygen fluctuation also causes mitochondrial dysfunction that increases oxidative stress. Therefore, maintaining a target oxygen saturation between SpO_2 90-95% has been shown to reduce the risk of ROP. On the other hand, hyperoxygenation SpO_2 >97% should be avoided due to the above-mentioned effects. Standardized protocols for NICU (neonatal intensive care unit) aim to minimize oxygen fluctuation and reduce oxidative stress [23].

Influence of nutritional factors

DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) are two omega-3 fatty acids that are essential for retinal and neural development. Premature infants are deficient in these two fatty acids, as they pass from

the placenta to the fetus during the third trimester. The physiological role of EPA/DHA is seen in reducing proinflammatory mediators and promoting physiological angiogenesis. They reduce the overexpression of VEGF, thereby preventing excessive neovascularization and have a protective effect on endothelial cells from oxidative stress and apoptosis [24].

Molecules with antioxidant activity are crucial in dealing with oxidative stress. As previously mentioned, vitamins E, C and A and the enzymes – superoxide dismutase, catalase and glutathione peroxidase play an important role in this mechanism [20].

Genetic and epigenetic predisposition

The fact that not all premature infants develop ROP indicates the presence of additional genetic and epigenetic factors. Thus, polymorphisms in certain genes are considered to be a risk factor for the occurrence of ROP. Examples include[25, 26]:

a) The VEGF-A gene influences the level of VEGF production and blood vessel growth.
b) EPAS1 (HIF-2α gene) participates in the regulation of the response to hypoxia and influences the expression of VEGF.
c) CFH gene (Complement Factor H) is associated with a tendency to inflammation and oxidative stress in patients with ROP.

Epigenetic changes such as DNA methylation, histone modification and microRNA can influence gene expression without affecting DNA. Factors that are considered to influence these epigenetic changes are: hyperoxia/hypoxia, maternal nutrition, inflammation and infections (sepsis or chorioamnionitis)[27].

Potential biomarkers for early recognition of ROP

In recent years, there has been interest in finding useful biomarkers that would timely detect oxidative stress and damage in newborns. One of the main obstacles is to determine these biomarkers in different biological fluids such as: plasma, urine, amniotic fluid and cerebrospinal fluid. Since some of the free radicals and oxidation products have a short half-life, which makes it difficult to determine them. Several molecules have the potential to be possible biomarkers in patients with ROP [20]:

Malondialdehyde - a highly toxic molecule resulting from lipid peroxidation, a sensitive marker of oxidative stress that has been shown to be elevated in patients with ROP in several studies.

8-hydroxy 2-deoxyguanosine - a sensitive marker of oxidative DNA damage. Ates et al. found elevated values of this molecule in blood and urine samples of patients with ROP [28].

GSH/GSSG Ratio (oxidized/reduced glutathione ratio) is the most commonly used biomarker for determining oxidative stress. This ratio may be a useful parameter for early recognition of ROP in premature infants [20].

Protein oxidation - certain amino acids, e.g. phenylalanine, are susceptible to oxidation by ROS. As a result of this oxidation, certain molecules

are produced that can be used as markers of inflammation [29].

Lipid oxidation - the retina is quite susceptible to oxidative stress, through mechanisms of lipid peroxidation, a process that is involved in the pathogenesis of ROP. Polyunsaturated fatty acids are particularly susceptible to oxidation caused by free radicals, forming various by-products that can be identified as potential biomarkers in patients with ROP [22,29].

Clinical application and future perspectives

Knowledge of the links in the pathophysiological mechanism will lead to appropriate ROP screening guides for appropriate recognition and management of the condition. It should be noted that patients with ROP are at increased risk of other ophthalmological diseases throughout life such as: myopia, amblyopia, strabismus and retinal detachment 30. Therefore, timely visual rehabilitation is extremely important. The development of predictive biomarkers may in the future provide guidance on which patients are at increased risk for long-term ophthalmological problems. Knowledge of the pathogenesis of the disease should enable the creation of biomarkers that will allow personalization of ROP treatment in order to achieve optimal outcomes for each patient.

Artificial intelligence has the potential in the future to enable better automated screening and staging of the disease. This will provide predictive guidance for disease progression and appropriate treatment. Telemedicine, on the other hand, has the potential to help in less developed regions for timely recognition and treatment of the condition[31].

Conclusion

To date, ROP still represents a major challenge for both neonatologists and ophthalmologists dealing with this pathology. It represents a complex multifactorial process driven by a large number of proinflammatory components, impaired angiogenic signaling, and oxygen dysregulation. Ongoing research should help in understanding the details of the pathophysiological mechanism of this disease, all in order to enable new potential therapeutic modalities and different biomarkers that will help in better management of the disease.

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