ISSN 2218-6239 (online)

World Journal of *Ophthalmology*

World J Ophthalmol 2013 November 12; 3(4): 32-40

Baishideng Publishing Group
www.wjgnet.com

WJO World Journal of Ophthalmology

A peer-reviewed, online, open-access journal of ophthalmology

Editorial Board

2011-2015

The *World Journal of Ophthalmology* Editorial Board consists of 219 members representing a team of worldwide experts in ophthalmology. They are from 38 countries, Australia (7), Austria (1), Belgium (1), Brazil (4), Bulgaria (1), Canada (4), China (14), Czech Republic (1), Egypt (5), Finland (1), France (2), Germany (5), Greece (5), India (12), Iran (6), Israel (6), Italy (11), Japan (12), Kuwait (1), Lebanon (1), Mexico (2), Netherlands (3), Nigeria (2), Norway (1), Oman (1), Pakistan (1), Palestine (1), Poland (2), Portugal (1), Saudi Arabia (4), Singapore (4), South Korea (6), Spain (10), Switzerland (1), Thailand (1), Turkey (9), United Kingdom (11), and United States (59).

Vinod Kumar, *New Delhi*
Padmamalini Mahendradas, *Bangalore*
Gaurav Prakash, *Chennai*
Manikandan Ramar, *Karaikudi*
Velpandian Thirumurthy, *New Delhi*
Murugesan Vanathi, *New Delhi*
Pradeep Venkatesh, *New Delhi*
Sharadini Vyas, *Indore*

Iran

Sepehr Feizi, *Tehran*
Fedra Hajizadeh, *Tehran*
Ebrahim Mikaniki, *Babol*
Mehrdad Mohammadpour, *Tehran*
Mohammad Taher Rajabi, *Tehran*
M Reza Razeghinejad, *Shiraz*

Israel

Irit Bahar, *Petach Tiqva*
Adiel Barak, *Tel Aviv*
Guy Kleinmann, *Rehovot*
Jaime Levy, *Beer-Sheva*
Anat Loewenstein, *Tel Aviv*
Naphtali Savion, *Tel Hashomer*

Italy

Solmaz Abdolrahimzadeh, *Rome*
Stefano Baldassi, *Florence*
Vanessa Barbaro, *Venice*
Claudio Campa, *Milano*
Gian Carlo Demontis, *Pisa*
Giuseppe Lo Giudice, *Padova*
Marco Guzzo, *Milan*
Pierluigi Iacono, *Rome*
Antonio Leccisotti, *Siena*
Cosimo Mazzotta, *Siena*
Luigi Mosca, *Rome*

Japan

Atsushi Hayashi, *Toyama*
Akira Hirata, *Saga*
Yoshihiro Hotta, *Hamamatsu*
Hiroshi Kobayashi, *Shimonoseki*
Toshinobu Kubota, *Nagoya*
Shigeki Machida, *Iwate*
Tatsuya Mimura, *Tokyo*
Kazuno Negishi, *Tokyo*
Sakamoto Taiji, *Kagoshima*
Yoshihiko Usui, *Tokyo*
Tsutomu Yasukawa, *Nagoya*
Shigeo Yoshida, *Fukuoka*

Kuwait

Hanan El-Sayed Badr, *Kuwait*

Lebanon

Haytham Ibrahim Salti, *Beirut*

Mexico

Federico Castro-Munozledo, *Mexico City*
Alejandro Navas, *Mexico City*

Netherlands

Hoyng Carel Benedict, *Nijmegen*
AI den Hollander, *Nijmegen*
Jeroen van Rooij, *Rotterdam*

Nigeria

Opeyemi Olufemi Komolafe, *Owo*
Caleb Damilep Mpyet, *Jos*

Norway

Morten C Moe, *Oslo*

Oman

Mohamed AM Mahdy, *Bur Al-Rudah*

Pakistan

Raheel Qamar, *Islamabad*

Palestine

Sharif A Issa, *Gaza*

Poland

Michal Szymon Nowak, *Lodz*
Bartosz L Sikorski, *Bydgoszcz*

Portugal

Joaquim Carlos Neto Murta, *Coimbra*

Saudi Arabia

Khaled Khader Abu-Amero, *Riyadh*
Hind Manaa Alkatan, *Riyadh*
J Fernando Arevalo, *Riyadh*
Celia Chen, *Celia*

Singapore

Leonard Pek-Kiang Ang, *Singapore*
Gemmy Chui Ming Cheung, *Singapore*
Philip Francis Stanley, *Singapore*
Louis-MG Tong, *Singapore*

South Korea

Young Jae Hong, Seoul
Hakyoung Kim, *Seoul*
Jae Woong Koh, *Gwangju*
Sung Chul Lee, *Seoul*
Ki Ho Park, *Seoul*
Kyung Chul Yoon, *Gwangju*

Spain

Mercedes Hurtado-Sarrio, *Valencia*
Gonzalez GL Ignacio, *Madrid*
Antonio B Martinez, *Ames*
Javier A Montero-Moreno, *Valladolid*
Amparo Navea-Tejerina, *Valencia*
Julio Ortega-Usobiaga, *Bilbao*
Isabel Pinilla, *Zaragoza*
Jaime Tejedor, *Madrid*
Manuel Vidal-Sanz, *Espinardo*
Vicente Zanon-Moreno, *Valencia*

Switzerland

David Goldblum, *Basel*

Thailand

Weekitt Kittisupamongkol, *Bangkok*

Turkey

Ipek Akman, *Istanbul*
Dilek Dursun Altinors, *Ankara*
Gokhan Ibrahim Gulkilik, *Istanbul*
Necip Kara, *Istanbul*
Peykan Turkcuoglu, *Malatya*
Mustafa Unal, *Antalya*
Fatime Nilufer Yalcindag, *Ankara*
Elvin Hatice Yildiz, *Ankara*

United Kingdom

GB Arden, *London*
Allon Barsam, *London*
Ngaihang Victor Chong, *Oxford*
Ahmed N El-Amir, *Berkshire*
Mostafa A Elgohary, *London*
Bhaskar Gupta, *Exeter*
Adeela Malik, *Essex*
Colm McAlinden, *Londonderry*
Fiona Rowe, *Liverpool*
Om P Srivastava, *Birmingham*
Stephen Andrew Vernon, *Nottingham*

United States

Juan-Carlos Abad, *Colombia*
Hind Manaa Alkatan, *Galveston*
John Palmer Berdahl, *Sioux Falls*
John David Bullock, *Dayton*
David J Calkins, *Nashville*
Michelle C Callegan, *Oklahoma*
Marissa Janine Carter, *Cody*
Robert Jin-Hong Chang, *Champaign*
Imtiaz A Chaudhry, *Houston*
Yan Chen, *Nashville*
Shravan Chintala, *Rochester*

WJO

World Journal of Ophthalmology

Contents

Quarterly Volume 3 Number 4 November 12, 2013

Contents

World Journal of Ophthalmology
Volume 3 Number 4 November 12, 2013

AIM AND SCOPE

World Journal of Ophthalmology (*World J Ophthalmol*, *WJO*, online ISSN 2218-6239, DOI: 10.5318) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJO covers topics concerning optometry, ocular fundus diseases, cataract, glaucoma, keratopathy, ocular trauma, strabismus, and pediatric ocular diseases, blindness prevention, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of ophthalmological diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

NAME OF JOURNAL
World Journal of Ophthalmology

ISSN
ISSN 2218-6239 (online)

LAUNCH DATE
December 30, 2011

FREQUENCY
Quarterly

World Journal of Ophthalmology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-6555-7188
Telephone: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
November 12, 2013

World Journal of Ophthalmology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5318/wjo.v3.i4.32

World J Ophthalmol 2013 November 12; 3(4): 32-37
ISSN 2218-6239 (online)

MINIREVIEWS

Melatonin and derivatives as promising tools for glaucoma treatment

Hanan Awad Alkozi, Jesús Pintor

Hanan Awad Alkozi, Jesús Pintor, Department of Biochemistry and Molecular Biology IV, Faculty of Optics and Optometry, Universidad Complutense de Madrid, E-28037 Madrid, Spain
Author contributions: Alkozi HA and Pintor J contributed equally to this work.
Supported by Universidad Complutense de Madrid, No. GR35/10-A-920777; the Ministry of Economy, No. SAF 2010/16024; the Institute Carlos III, No. RETICS RD12/0034/0003
Correspondence to: Jesús Pintor, Professor, Department of Biochemistry and Molecular Biology IV, Faculty of Optics and Optometry, Universidad Complutense de Madrid, c/Arcos de Jalón 118, E-28037 Madrid, Spain. jpintor@ucm.es
Telephone: +34-91-3946859 Fax: +34-91-3946885
Received: August 21, 2013 Revised: November 5, 2013
Accepted: November 10, 2013
Published online: November 12, 2013

Key words: 5-MCA-NAT; IIK7; Glaucoma; Ocular hypertension; Melatonin

Core tip: This mini review depicts the main features of melatonin and derivatives as interesting agents for the treatment of the ocular hypertension associated with glaucoma.

Alkozi HA, Pintor J. Melatonin and derivatives as promising tools for glaucoma treatment. *World J Ophthalmol* 2013; 3(4): 32-37 Available from: URL: http://www.wjgnet.com/2218-6239/full/v3/i4/32.htm DOI: http://dx.doi.org/10.5318/wjo.v3.i4.32

Abstract

Neurohormones melatonin and its analogues are present with an important physiological and pharmacological ability to reduce intraocular pressure (IOP); thus, they are suitable for the treatment of ocular hypertension often associated with glaucoma. It is demonstrated that two of its analogues, 5-MCA-NAT and IIK7, are more effective than melatonin to reduce IOP for a longer period of time. The research for the discovery of better compounds resulted in the development of newer and improved analogues compared to 5-MCA-NAT and IIK7. Furthermore, already commercially available drugs currently used as treatment for other pathologies, presenting a resemblance to the melatonin structure, are being tested as potential glaucoma drugs. In this sense, agomelatine, which is already used as an anti-depressant medicine, is recognized as a worthy candidate since it reduces IOP, even under hypertensive conditions. To sum up, the use of melatonin and its analogues as promising anti-glaucomatous substances is of great importance and should be given serious consideration.

INTRODUCTION

There is a general interest in searching for novel compounds capable of reducing intraocular pressure (IOP) as an improved alternative to the existing drugs. IOP can be lowered through the reduction of aqueous humor production or by increasing its outflow through the trabecular meshwork or uveoscleral pathways. The interest for searching for new compounds relies on the fact that most of the existing drugs produce important side effects, hampering the treatment of certain patients. Side effects are a common issue in glaucoma medications. β-blockers such as timolol can cause bradycardia and hypotension and they are unsuitable for patients suffering from cardio vascular problems[1], asthma, obstructive pulmonary disease or corneal dystrophy[2]. Cholinergic agonists such as pilocarpine produce fixed pupils and induce myopia and cataracts[1], whereas prostaglandins (*e.g.*, latanoprost) cause eyelash growth, iris pigmentation[3], muscle and joint pain[2]. Frequently, ocular redness and ocular surface discomfort obligates patients to abandon the treatment.

Several new compounds and approaches are under development in companies' pipelines or in academic institutions. Among the plethora of substances, the naturally occurring are more attractive as its administration is expected to result in fewer side effects[4]. Among these, the neurohormone melatonin emerges as a promising substance with interesting hypotensive properties[5]. The use of 5-MCA-NAT (a melatonin analogue, see below) when applied to the eye does not produce severe side effects. It does not affect corneal and lens transparency nor cause redness or corneal edema. No negative effects were noticed in general ocular examinations[5]. It is important to bear in mind that most of melatonin intake is not by prescription as it is considered a dietetic supplement. In this case, high dosages and an elevated number of intakes could produce some minor side effects. The Mayo Clinic indicates that the most common side effects are drowsiness, headache and dizziness. Moreover, large doses of melatonin can interfere with some medications, such as anticoagulants, immunosuppressants, diabetes medications and birth control pills.

There are two interesting works describing the melatonin effect and its analogues on reducing IOP. Serle *et al*[6] demonstrated that a melatonin analogue was able to reduce IOP in glaucomatous monkeys, suggesting these molecules as a possible treatment of ocular hypertension related to glaucoma. Additionally, a group of ophthalmologists started to use melatonin during cataract surgery because it reduces IOP substantially, which is recommendable during phacoemulsification[7].

From these two relevant works, the question arises as why these groups decided to use melatonin and its analogues for clinical purposes and mainly for reducing IOP. The present mini review introduces the reader to the basis of why melatonin is an attractive molecule to reduce IOP and why it should be considered in the future as a respectable alternative to the current ocular hypertension and glaucoma therapies.

MELATONIN, MORE THAN A PINEAL GLAND HORMONE

Melatonin is a molecule known by its chemical name N-acetyl-5-methoxytryptamine (Figure 1). It has been traditionally related to a particular area of brain, termed the pineal gland, where it is synthesized in low illumination conditions like during the night[8] and it regulates many day-night processes, called circadian rhythms[9]. It is necessary to emphasize that this substance is also synthesized in other tissues and ocular structures such as the retina, the ciliary body or the lens. This clearly suggests that melatonin can exert some local actions on the tissues where it is synthesized or in surrounding areas. Keeping in mind that melatonin is released by the lens or the ciliary body, its presence in the aqueous humor, modifying the physiology of these structures being bathed in the fluid, can be speculated about. Interestingly, one of the possible physiological processes to be modified is IOP. It is documented that in many animal models there are changes in IOP during the day (high IOP) and night (low IOP). It is possible that both processes are associated considering the circadian pattern of melatonin production. Consequently, we should study what happens if we topically apply melatonin during the day when IOP is high.

MELATONIN REGULATES INTRAOCULAR PRESSURE

When melatonin is topically applied at a single dose of 100 μmol/L in a volume of 10 μL, there is a transient reduction in IOP and values return quickly to initial figures in about 2 h[10]. This effect is similar to that of endogenous melatonin at night which reduces IOP. Despite the acquired hypotensive effect, the rapid return to normal pressure values suggests that either it is necessary to regulate the doses or to look for an alternative compound to produce a more sustained effect[11].

There are several commercially available melatonin analogues depicting similar behavior to melatonin. Two compounds present sharper and long lasting effects on reducing the IOP compared to melatonin. In particular, the compound N-butanoyl-2-2-methoxy-6H-isoindolo ([2,1-a]indol-11-yl) ethanamine (abbreviated as IIK7) has a hypotensive effect that lasts up to 7 hours and the compound 5-methylcarboxyamino-N-acetyltryptamine (also known as 5-MCA-NAT), which can reduce IOP for up to 9 h (Figure 1)[12]. Consequently, 5-MCA-NAT is more interesting since it presents a longer term effect with a significant reduction of IOP for up to 96 h. This remarkable effect has been taken into consideration as we indicate below[11] (Table 1).

5-MCA-NAT was tested in normotensive models as well as under hypertensive conditions, including glaucomatous monkeys (Table 1). Interestingly, the effects on the monkeys, a model closer to the human glaucomatous pathology, were extremely interesting. Compared to vehicle treatment, twice daily administration of 5-MCA-NAT for 5 d reduced IOP from 1 to 5 h after the first dose and the IOP-lowering effects were shown to last at least 18 h following administration, based on IOP measurements made after the fourth and eighth doses[6].

One interesting characteristic to take into account was that the ocular hypotensive effect of 5-MCA-NAT was enhanced by repeated dosing. The maximum reduction of IOP was acquired 3 h after each morning dose and was 10% on day 1, 15% on day 3, and 19% on day 5 (control = 100%). No adverse ocular or systemic side effects were observed during the 5 treatment days, suggesting that this compound could be used perfectly as ocular hypertension treatment[6] (Table 1).

IIK7 reduced intraocular pressure by acting through MT_2 melatonin receptors, presumably decreasing aqueous humor formation. Its effect is concentration dependent and it can reduce IOP 38.5% ± 3.2% when compared to controls (Table 1). It is important to notice that these

Table 1 Hypotensive effects of melatonin analogues: animal models, conditions and receptors involved

Compound species	IOP reduction	Receptor involved	Ref.
Melatonin			
Human	32.0%± 3.2%	Unknown	[7]
Rabbit	22.0% ± 1.6%	MT_2, MT_3	[10,11]
Mouse (glaucomatous)	33.4% ± 2.5%	MT_2	UD
5-MCA-NAT			
Monkey (hypertensive)	19.2% ± 2.1%	MT_3	[6]
Rabbit	42.5% ± 1.6%	MT_3	[10,11]
IIK7			
Rabbit	38.5% ± 3.2%	MT_2	[12]
INS48848			
Rabbit	36.0% ± 2.0%	MT_3	[22]
INS48852			
Rabbit	33.1% ± 1.4%	MT_2	[22]
INS48862			
Rabbit	26.0 V ± 1.3 V	MT_2	[22]
Agomelatine			
Rabbit			
Normotensive	20.8% ± 1.4%	MT_2	[25]
Hypertensive	68.8% ± 5.7%	MT_2	[25]

The values represent the mean ± SEM for the indicated compounds in the respective animal model. IOP: Intraocular pressure; UD: Unpublished data.

experiments have not been performed in glaucomatous monkeys yet but only in rabbits[12].

In summary, it seems that some compounds, such as melatonin, 5-MCA-NAT and IIK7, clearly reduce IOP. But what is the mechanism for this IOP reduction? What receptors activate these substances in order to produce the observed effects?

MELATONIN AND ITS ANALOGUES ACTIVATE MELATONIN RECEPTORS

Melatonin exerts its effect *via* membrane and nuclear receptors. The protein membrane receptors are better understood and until recently three proteins have been cloned. Two of these membrane receptors, termed MT_1 and MT_2, are melatonin receptors belonging to the 7-transmembrane G protein-coupled receptor family (GPCR). There have been claims that a third receptor exists, the MT_3 melatonin receptor, although it has not been cloned yet. Some authors have identified it as quinone reductase 2 (QR2), demonstrating features of a melatonin receptor in some animal models (for a review see[9]).

MT_1, MT_2 and the probable MT_3 melatonin receptors are present in several ocular structures, according to pharmacological, biochemical and immunological studies[13,14]. This evidence suggests that melatonin plays a role in physiological processes in ocular tissues, such as the modulation of IOP, and it has been documented that MT_2 and MT_3 are responsible for IOP reduction.

When melatonin, 5-MCA-NAT and IIK7 are applied to normotensive or hypertensive eyes, they produce a dissimilar IOP reduction, depending on the compound

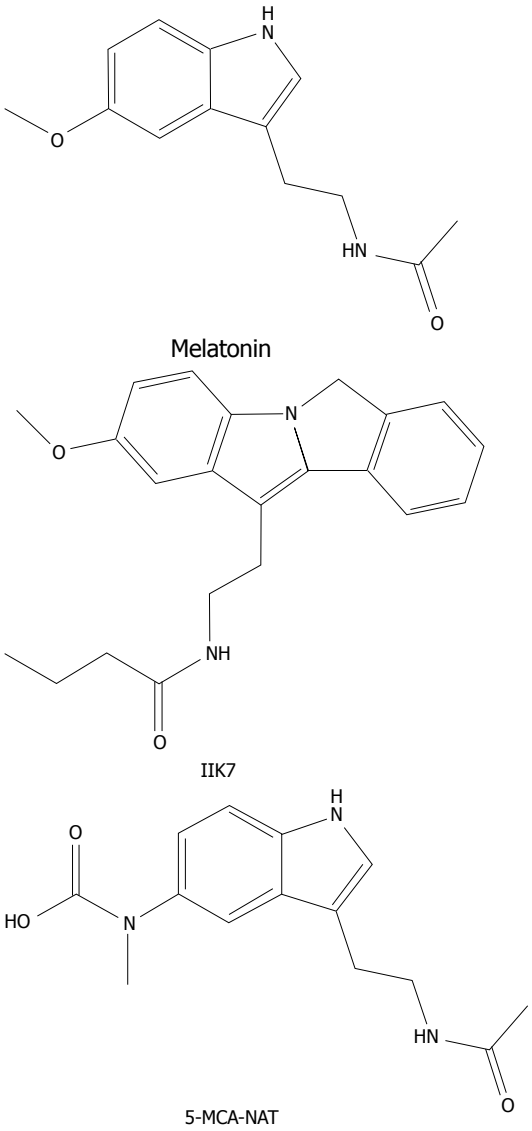

Figure 1 Chemical structure of melatonin and analogues. Melatonin (N-acetyl-5-methoxytryptamine), IIK7 (N-butanoyl-2-(2-methoxy-6H-isoindolo[2,1-a]indol-11-yl)ethanamine) and 5-MCA-NAT (5-methylcarboxyamino-N-acetyltryptamine).

under study. The use of selective antagonists for melatonin receptors has allowed identification of the presence of MT_2 melatonin receptors in the ciliary body of experimental animals, such as New Zealand white rabbits. This has been confirmed through immunohistochemical studies. In these studies it has been possible to verify the presence of MT_2 melatonin receptors on pigmented and non-pigmented ciliary epithelia. Accordingly, the application of melatonin or IIK7, which is a selective MT_2 agonist, results in a reduction in the production of the aqueous humor[12] (Figure 2).

5-MCA-NAT has been suggested as an MT_3 melatonin receptor agonist that reduces IOP. To date, the location of the receptor is unknown. As there is a controversy with the possible identification of the MT_3 receptor which is tentatively identified in some animal models as QR_2, some sophisticated experiments were performed to

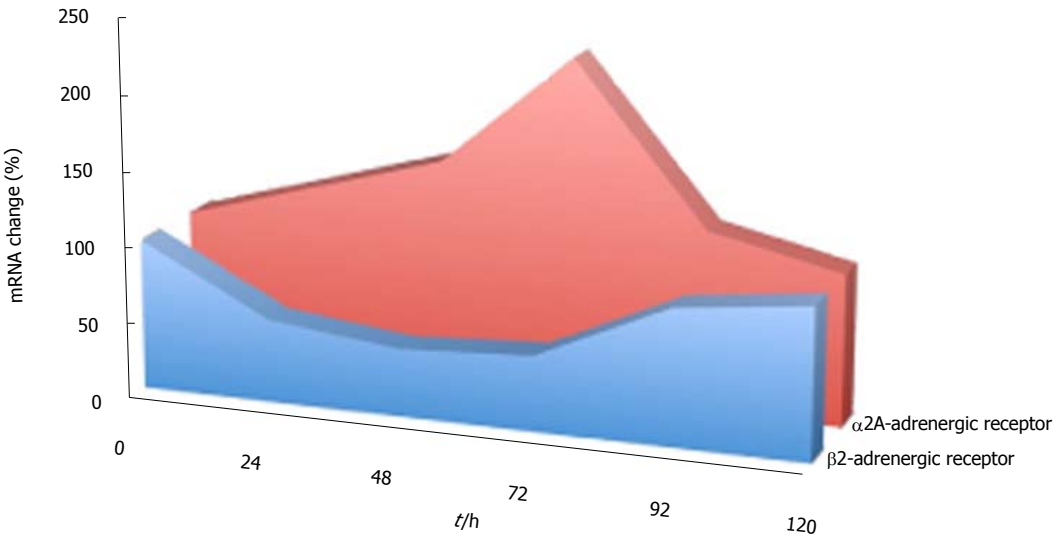

Figure 2 Expression of mRNA levels in ciliary body cells. The amounts of mRNA and concomitant adrenoceptors were changed after the application of 5-MCA-NAT. While there was an increase of α2A-adrenoreceptors (in red), there was a decrease in the levels of β2-adrenoreceptors (in blue).

clarify the issue[15-17]. In New Zealand rabbits, the use of a siRNA silencing QR_2 (therefore avoiding the expression of this enzyme) did not abolish the hypotensive effect of 5-MCA-NAT, clearly indicating that, in this animal model, $MT_3 \neq QR_2$, opening the possibility of speculating about the existence of a receptor that needs to be cloned to fully understand its functioning and location[18].

Apart from melatonin and its derivatives, some other compounds, like 5-MCA-NAT, can keep IOP below normal values for up to 5 d. This long-term effect is mediated by the action of melatonin receptors on the expression of genes expressing proteins important for the homeostasis of the aqueous humor.

To date, it has been possible to demonstrate that the 5-MCA-NAT long-term effect is in part the result of the expression inhibition of carbonic anhydrases. This down-regulation means that 24 h after 5-MCA-NAT application there is a reduction in IOP because the amounts of carbonic anhydrases are severely reduced. In particular, when 5-MCA-NAT is applied, carbonic anhydrase 2 is reduced 32% (protein levels), while carbonic anhydrase 12 is reduced 39% (protein levels). This reduction in protein expression mimics the carbonic anhydrase inhibitor action, such as dorzolamide or acetazolamide[19].

Likewise, the expression of adrenergic receptors is modified by the application of 5-MCA-NAT. Interestingly, this melatonin analogue is able to produce a sequential process consisting of an initial reduction in the β2-adrenoreceptors expression, followed by an increase in α2A-adrenoreceptors[20]. Altogether, these consecutive effects produce a sustained reduction in IOP lasting for at least 96 h[21].

In summary, 5-MCA-NAT, apart from a sharp hypotensive effect, exerts a long term effect, maintaining low IOP for 4 d.

SO, WHAT IS NEXT NOW?

Several aspects need to be studied, taking into account that melatonin and analogues can significantly reduce IOP.

It is clear that it is necessary to research and design new melatonin analogues with more profound and long lasting effects[5]. Inspire Pharmaceuticals Inc. (now absorbed by Merck) has designed several melatonin analogues with interesting hypotensive properties to reduce IOP. In recent studies, melatonin analogues, termed INS48848, INS48852 and INS48862, demonstrated similar behavior to melatonin, 5-MCA-NAT and IIK7[22]. Indeed, these three compounds decreased IOP in a dose-dependent manner similar to melatonin, 5-MCA-NAT and IIK7, confirming their efficiency in decreasing IOP (Table 1). Concerning their selectivity on melatonin receptors, the effects of INS48848 were completely blocked by prazosin, an antagonist of MT_3 melatonin receptors, and were potently inhibited by luzindole, a non-selective antagonist of melatonin receptors. However, DH97, a selective MT_2 receptor antagonist, had a limited effect against INS48848 and the results obtained from INS48862 and INS48852 were contradictory. Luzindole and prazosin had no significant effects against those two compounds, whereas DH97 blocked them completely. These results strongly suggest that INS48848 could be acting through the MT_3 melatonin receptors and that INS48862 and INS48852 could be acting preferentially through MT_2 melatonin receptors. In any case, all these compounds are worthy candidates to reduce IOP, especially when it is abnormally elevated[22].

Another alternative to the development of newly synthesized compounds is to search for melatoninergic compounds already used for other medical purposes. Compounds such as ramelteon ((S)-N-[2-(1,6,7,8-tetrahyd-

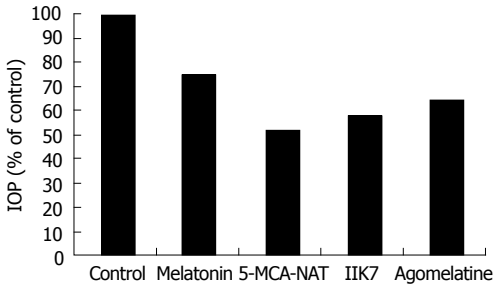

Figure 3 Comparative effects of melatonin and analogues in an animal model. Equal doses of melatonin or the corresponding analogues (100 μmol/L, 10 μL), reduced intraocular pressure in New Zealand white rabbits. Differences among the compounds rely on the activation of different receptors in each case (see text).

ro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide), also known as *Rozerem*, used for sleep disorders[23] or agomelatine (N-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide), known also by the names *Valdoxan, Melitor, Thymanax*[24], used for the treatment of depression, could be candidates to reduce IOP since their structure is similar to melatonin.

There is a lack of information regarding the use of ramelteon in IOP studies. Agomelatine significantly reduces IOP when topically applied on rabbit eyes. Agomelatine (10 μL, 100 μmol/L) reduced IOP by 20.8% ± 1.4% and its maximal IOP reduction was 180 minutes after the compound application. Interestingly, this compound exhibited an ability to reduce IOP in hypertensive conditions. It is noteworthy to stress that under high IOP the ability of this melatonin analogue to reduce IOP was 68.8% ± 5.7% (Figure 3, Table 1)[25].

There is a clear advantage in using compounds already commercialised for other conditions as the timeline for testing and clinical trials is significantly reduced.

CONCLUSION

It is necessary to perform an exhaustive study on the role of melatonin and its analogues in the different ocular structures since it is very probable that this knowledge will contribute to the discovery of more effective treatments for pathologies like glaucoma, corneal wound healing, cataracts or retinal pathology[26].

Taking into account the importance of the role of melatonin and its analogues in hypertension, often associated with glaucoma, it is quite evident that these compounds should be used as treatment to reduce IOP. Melatonin or agomelatine can simply and rapidly reduce IOP, although further research is required to prove that they can be safely used as treatment for ocular hypertension.

Most of the presented data resulted from experiments assaying melatonin or its analogues on animal models. We still have a long way to go to test these compounds on human beings. Nevertheless, there are a lot of positive points regarding the efficacy of certain melatoninergic compounds. For instance, melatonin itself is able to reduce IOP in normotensive humans, as previously described[7]. These authors reported an approximate 30% reduction in IOP during cataract surgery compared to the initial patient's pressures. This is quite interesting because the IOP reduction has been obtained in normotensive patients and it could be even more substantial in hypertensive (glaucomatous) patients. Several experiments in animal models demonstrated that melatonin and analogues are able to reduce IOP equally in normotensive and hypertensive animals, being more effective in hypertensive than in normotensive animals (Table 1). Also, experiments performed with 5-MCA-NAT on hypertensive monkeys, a step before human clinical trials, have proved that this melatonin analogue reduced IOP.

In conclusion, agomelatine is the compound that we strongly believe should be tested in glaucomatous patients for its ability to reduce IOP. Agomelatine is already used as a depression treatment drug under the commercial name Valdoxan[24]. Since many of the pre-clinical tests have already been completed, we should not be surprised if agomelatine clinical trials start and it becomes the first melatoninergic compound to join the group of glaucoma treatment substances.

ACKNOWLEDGEMENTS

The Harvard Alumni Association is a fellowship holder of Saudi Arabia Government.

REFERENCES

1 **Hoyng PF**, van Beek LM. Pharmacological therapy for glaucoma: a review. *Drugs* 2000; **59**: 411-434 [PMID: 10776828 DOI: 10.2165/00003495-200059030-00003]
2 **Higginbotham EJ**, Schuman JS, Goldberg I, Gross RL, VanDenburgh AM, Chen K, Whitcup SM. One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. *Arch Ophthalmol* 2002; **120**: 1286-1293 [PMID: 12365906 DOI: 10.1001/archopht.120.10.1286]
3 **Johnstone MA**. Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. *Am J Ophthalmol* 1997; **124**: 544-547 [PMID: 9323945]
4 **Mediero A**, Alarma-Estrany P, Pintor J. New treatments for ocular hypertension. *Auton Neurosci* 2009; **147**: 14-19 [PMID: 19176290 DOI: 10.1016/j.autneu.2008.12.009]
5 **Crooke A**, Colligris B, Pintor J. Update in glaucoma medicinal chemistry: emerging evidence for the importance of melatonin analogues. *Curr Med Chem* 2012; **19**: 3508-3522 [PMID: 22709004 DOI: 10.2174/092986712801323234]
6 **Serle JB**, Wang RF, Peterson WM, Plourde R, Yerxa BR. Effect of 5-MCA-NAT, a putative melatonin MT3 receptor agonist, on intraocular pressure in glaucomatous monkey eyes. *J Glaucoma* 2004; **13**: 385-388 [PMID: 15354076 DOI: 10.1097/01.ijg.0000133150.44686.0b]
7 **Ismail SA**, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. *Anesth Analg* 2009; **108**: 1146-1151 [PMID: 19299777 DOI: 10.1213/ane.0b013e3181907ebe]
8 **Ackermann K**, Stehle JH. Melatonin synthesis in the human pineal gland: advantages, implications, and difficulties. *Chronobiol Int* 2006; **23**: 369-379 [PMID: 16687310 DOI: 10.1080/07420520500464379]
9 **Alarma-Estrany P**, Pintor J. Melatonin receptors in the eye: location, second messengers and role in ocular physiology. *Pharmacol Ther* 2007; **113**: 507-522 [PMID: 17229466 DOI:

10.1016/j.pharmthera.2006.11.003]
10 **Pintor J**, Martin L, Pelaez T, Hoyle CH, Peral A. Involvement of melatonin MT(3) receptors in the regulation of intraocular pressure in rabbits. *Eur J Pharmacol* 2001; **416**: 251-254 [PMID: 11290376 DOI: 10.1016/S0014-2999(01)00864-0]
11 **Pintor J**, Peláez T, Hoyle CH, Peral A. Ocular hypotensive effects of melatonin receptor agonists in the rabbit: further evidence for an MT3 receptor. *Br J Pharmacol* 2003; **138**: 831-836 [PMID: 12642384 DOI: 10.1038/sj.bjp.0705118]
12 **Alarma-Estrany P**, Crooke A, Mediero A, Peláez T, Pintor J. Sympathetic nervous system modulates the ocular hypotensive action of MT2-melatonin receptors in normotensive rabbits. *J Pineal Res* 2008; **45**: 468-475 [PMID: 18673419 DOI: 10.1111/j.1600-079X.2008.00618.x]
13 **Dubocovich ML**. Pharmacology and function of melatonin receptors. *FASEB J* 1988; **2**: 2765-2773 [PMID: 2842214]
14 **Dubocovich ML**, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. *Endocrine* 2005; **27**: 101-110 [PMID: 16217123 DOI: 10.1385/ENDO:]
15 **Boutin JA**, Saunier C, Guenin SP, Berger S, Moulharat N, Gohier A, Delagrange P, Cogé F, Ferry G. Studies of the melatonin binding site location onto quinone reductase 2 by directed mutagenesis. *Arch Biochem Biophys* 2008; **477**: 12-19 [PMID: 18502195 DOI: 10.1016/j.abb.2008.04.040]
16 **Mailliet F**, Ferry G, Vella F, Berger S, Cogé F, Chomarat P, Mallet C, Guénin SP, Guillaumet G, Viaud-Massuard MC, Yous S, Delagrange P, Boutin JA. Characterization of the melatoninergic MT3 binding site on the NRH: quinone oxidoreductase 2 enzyme. *Biochem Pharmacol* 2005; **71**: 74-88 [PMID: 16293234 DOI: 10.1016/j.bcp.2005.09.030]
17 **Tan DX**, Manchester LC, Terron MP, Flores LJ, Tamura H, Reiter RJ. Melatonin as a naturally occurring co-substrate of quinone reductase-2, the putative MT3 melatonin membrane receptor: hypothesis and significance. *J Pineal Res* 2007; **43**: 317-320 [PMID: 17910598 DOI: 10.1111/j.1600-079X.2007.00513.x]
18 **Alarma-Estrany P**, Crooke A, Pintor J. 5-MCA-NAT does not act through NQO2 to reduce intraocular pressure in New-Zealand white rabbit. *J Pineal Res* 2009; **47**: 201-209 [PMID: 19627460 DOI: 10.1111/j.1600-079X.2009.00702.x]
19 **Crooke A**, Huete-Toral F, Martínez-Águila A, Martín-Gil A, Pintor J. Involvement of carbonic anhydrases in the ocular hypotensive effect of melatonin analogue 5-MCA-NAT. *J Pineal Res* 2012; **52**: 265-270 [PMID: 22107075 DOI: 10.1111/j.1600-079X.2011.00938.x]
20 **Crooke A**, Huete-Toral F, Martínez-Águila A, Alarma-Estrany P, Pintor J. Regulation of ocular adrenoceptor genes expression by 5-MCA-NAT: implications for glaucoma treatment. *Pharmacogenet Genomics* 2011; **21**: 587-589 [PMID: 21705965 DOI: 10.1097/FPC.0b013e32834910d1]
21 **Crooke A**, Huete-Toral F, Martínez-Águila A, Martín-Gil A, Pintor J. Melatonin and its analog 5-methoxycarbonylamino-N-acetyltryptamine potentiate adrenergic receptor-mediated ocular hypotensive effects in rabbits: significance for combination therapy in glaucoma. *J Pharmacol Exp Ther* 2013; **346**: 138-145 [PMID: 23591996 DOI: 10.1124/jpet.112.202036]
22 **Alarma-Estrany P**, Guzman-Aranguez A, Huete F, Peral A, Plourde R, Pelaez T, Yerxa B, Pintor J. Design of novel melatonin analogs for the reduction of intraocular pressure in normotensive rabbits. *J Pharmacol Exp Ther* 2011; **337**: 703-709 [PMID: 21368006 DOI: 10.1124/jpet.110.178319]
23 **Laustsen G**, Andersen M. Ramelteon (rozerem) a novel approach for insomnia treatment. *Nurse Pract* 2006; **31**: 52-55 [PMID: 16607213 DOI: 10.1097/00006205-200604000-00011]
24 **Millan MJ**, Brocco M, Gobert A, Dekeyne A. Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. *Psychopharmacology* (Berl) 2005; **177**: 448-458 [PMID: 15289999 DOI: 10.1007/s00213-004-1962-z]
25 **Martínez-Águila A**, Fonseca B, Bergua A, Pintor J. Melatonin analogue agomelatine reduces rabbit's intraocular pressure in normotensive and hypertensive conditions. *Eur J Pharmacol* 2013; **701**: 213-217 [PMID: 23270715 DOI: 10.1016/j.ejphar.2012.12.009]
26 **Crooke A,** Huete-Toral F, Martínez-Águila A, Colligris B, Pintor J. Ocular disorders and the utility of animal models in the discovery of melatoninergic drugs with therapeutic potential. *Expert Opin Drug Discov* 2012; **7**: 989-1001 [PMID: 22860991 DOI: 10.1517/17460441.2012.714769]

P- Reviewers: Clement CI, Hong YJ, Nowak MS, Zanon-Moreno V
S- Editor: Song XX **L- Editor:** Roemmele A
E- Editor: Lu YJ

World Journal of Ophthalmology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5318/wjo.v3.i4.38

World J Ophthalmol 2013 November 12; 3(4): 38-40
ISSN 2218-6239 (online)

CASE REPORT

Multifocal granulomata in presumed Toxocara canis infection in adult

Lakshmi Kuniyal, Jyotirmay Biswas

Lakshmi Kuniyal, Department of Vitreoretina, Sankara Nethralaya, Chennai, TN 600006, Andhra Pradesh, India
Jyotirmay Biswas, Department of Uvea, Sankara Nethralaya, Chennai, TN 600006, Andhra Pradesh, India
Author contributions: Kuniyal L and Biswas J contributed equally to this work.
Correspondence to: Dr. Lakshmi Kuniyal, MS, Department of Vitreoretina, Sankara Nethralaya, Pycrofts Garden Road, Chennai, TN 600006, Andhra Pradesh, India. dr.meen2105@gmail.com
Telephone: +91-98-71076396 Fax: +91-98-71076396
Received: October 11, 2013 Revised: November 1, 2013
Accepted: November 5, 2013
Published online: November 12, 2013

Abstract

Human infection of Toxocara canis in eye is usually an outcome of accidental ingestion of the embryonated eggs. The average age at diagnosis of ocular Toxocariasis is 7.5 years, ranging from 2 to 31 years. It constitutes 1%-2% of uveitis in children. Diagnosis is based upon the clinical features observed in a young patient and confirmed by the presence of specific IgG in the serum or aqueous humor by Enzyme-linked immunosorbent assay test. We report a case of Presumed Toxocara infection in 45-year-old male which is unique in presentation with multifocal granulomata in retina. Our PubMed search could not produce case with similar presentation. Probably this is the first reported case of multifocal granulomata in presumed ocular Toxocara in any age group

Key words: Presumed; Toxocara canis; Ocular; Multifocal; Granulomata

Core tip: Toxocara infection is one of the causes of posterior uveitis. Diagnosis is often made by presence of larvae in the choroidal granuloma. The aim of this study is to focus on the diagnosis of case where presence of multifocal granuloma and absence of larvae in granulaoma makes the diagnosis atypical. A combination of history, clinical examination, laboratory tests and histopathological analysis is important before reaching any diagnosis.

Kuniyal L, Biswas J. Multifocal granulomata in presumed Toxocara canis infection in adult. *World J Ophthalmol* 2013; 3(4): 38-40 Available from: URL: http://www.wjgnet.com/2218-6239/full/v3/i4/38.htm DOI: http://dx.doi.org/10.5318/wjo.v3.i4.38

INTRODUCTION

The larva of the nematode Toxocara canis was first identified as a cause of intraocular disease by Nichols (1956). Human infection is usually an outcome of accidental ingestion of the embryonated eggs[1]. The average age at diagnosis of ocular Toxocariasis is 7.5 years (ranging from 2 to 31 years). It constitutes about 1%-2% of uveitis in children[2]. Toxocara should be considered as a possible causative agent of posterior uveitis. Diagnosis is based upon clinical features observed in a young patient and should be confirmed at least by the presence of specific IgG in the serum (ELISA test, 90% specificity and 91% sensitivity)[3]. We present here presumed ocular Toxocara infection in a 45 year adult. The case is unique for its presentation at this age and multifocal granulomata on retinal evaluation. PubMed search could not reveal presence of multifocal granulomata in ocular Toxocara infection before.

CASE REPORT

A 45-year-old male presented with complaints of gradually progressive diminution of vision since one and half years in the left eye. There were no pets in the house. Patient was a known diabetic controlled on oral hypogly-

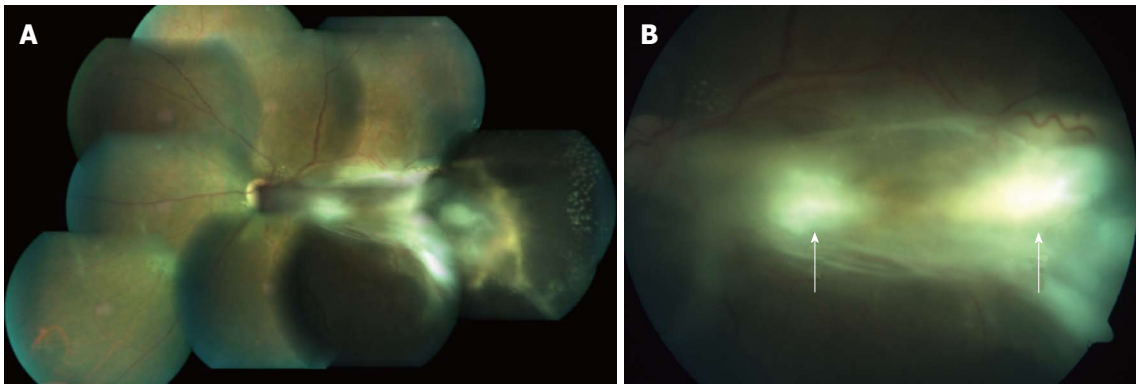

Figure 1 Fundus photo of patient' right eye. A: Montage colour fundus photo of patient showing extent of lesion with multifocal granulomata and temporal exudative retinal detachment; B: Fundus photo showing granulomata.

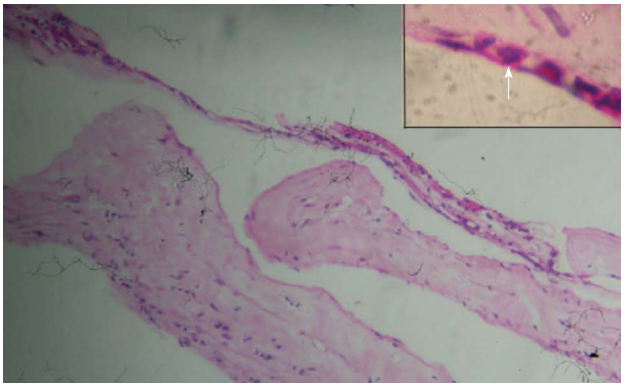

Figure 2 Haematoxylin and Eosin staining X 200: Micro photograph showing an epiretinal membrane with chronic inflammatory cells comprising of lymphocytes Inset: Shows few eosinophils (arrow). No larva seen.

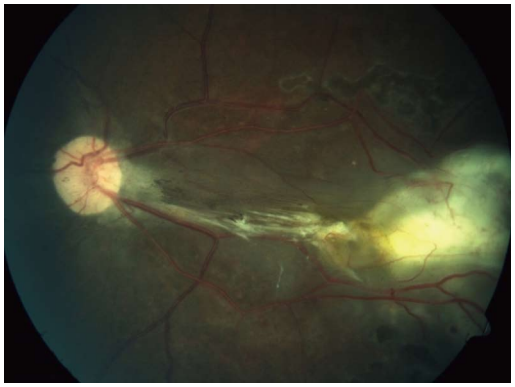

Figure 3 Post operative fundus photograph showing scar extending from disc to temporal periphery.

cemic agents. At presentation his corrected visual acuity in right eye was 6/5 for distance with near vision N6 and left eye had counting finger for distance with near vision < N36 on snellens chart. Anterior segment findings were within normal limits. Right eye fundus was within normal limits whereas left eye fundus showed fibrous membranous band extending from optic nerve head to temporal periphery with subretinal exudation and exudative retinal detachment temporally (Figure 1). The unique thing about this lesion was that it covered area from posterior pole to far temporal periphery and showed multifocal choroidal granulomata which are very unusual of Toxocara granuloma (Figure 1). Investigation revealed positive IgE titer of Toxocara in anterior chamber tap (16.93NTU). Optical coherence tomography showed macular traction with increased retinal thickness. Patient was started on oral steroids and planned for surgery. Vitrectomy with membrane peeling was done. Silicone oil was injected when break occurred while removing adherent membrane. Histopathological analysis of the membrane showed fibrous tissue with chronic inflammatory cells. No Toxocara parasite was seen. On careful examination few eosinophils were seen (Figure 2). After 6 wk of surgery retina was attached with scarring extending from disc to temporal periphery. Patient had vision of counting finger which was due to scarring (Figure 3). Patient was doing well on ten weeks of follow up.

DISCUSSION

Ocular Toxocariasis usually occurs in young healthy children. It is usually limited to one eye and infected by one larva (Schlaegel, 1978)[4]. There are few clinical reports of retinal lesions in adults due to Toxocara infection. Larva is rarely identified from the lesions. Definitive histopathological diagnosis is possible only after enucleation. Because of the absence of larva on histopathology, we refer our case as Presumed Ocular Toxocariasis.

Ocular involvement can occur in form of chronic endophthalmitis, papillitis, posterior pole granuloma and peripheral granuloma[1]. Patients with posterior pole granuloma may initially present with relatively hazy vitreous body and sign of acute inflammation, in which the posterior pole granuloma is observed as an ill-defined hazy mass with surrounding vitreous inflammation. These lesions are usually very well-defined and relatively small, ranging from 0.75 to 6.0 mm in diameter in size. In peripheral granuloma, a dense white peripheral inflammatory granulomatous mass is localized. Alternatively, the inflammation may be diffuse and appears as a "snowbank" as seen in pars planitis. Fibrocellular bands may run from

a peripheral inflammatory mass to posterior retina or the optic nerve leading to both traction and rhegmatogenous retinal detachment[5].

Our patient presented with combined picture of posterior and peripheral granuloma with multifocal granulomata. The presence of multifocal granulomata in our patient was unusual and probably the first time reported.

The major causes of visual acuity loss are: severe vitritis (52.6% of the cases), cystoid macular edema (47.4%) and tractional retinal detachment (36.8%)[6]. It is possible that the lesions are due to a toxic or immunoallergic reaction towards larval antigens, mainly associated with larval death. The disruption occurring after larval death may determine an inflammatory reaction and granuloma formation. We also found the presence of chronic inflammatory cells along with eosinophils confirming the inflammatory nature of the membrane.

Treatment therapy should be guided according to: visual acuity, severity of inflammation, irreversible ocular damage[1]. Generally peripheral granulomata are silent or show minimal inflammatory reaction and do not require therapy. Corticosteroid therapy helps to reduce the inflammatory process without permitting the overgrowth of the infectious agent. Antihelminthic therapy is not worldwide accepted because of the possibility that larvae death may increase the inflammatory reaction. Pars plana vitrectomy is useful and indicated to remove vitreous opacities and epiretinal membranes, to relieve the vitreoretinal traction, to prevent and treat retinal detachment[7,8].

In our patient we successfully removed the membranes despite its firm adherence to underlying tissue. The vision was counting finger because of scarring over posterior pole caused by the membrane.

A study with longer follow up is required to see how multifocal granulomata differ in prognosis from usual focal granuloma of Toxocara.

COMMENTS

Case characteristics

A 45-year-old male presented with complaints of gradually progressive diminution of vision since one and half years in the left eye.

Clinical diagnosis

Right eye fundus was within normal limits whereas left eye fundus showed fibrous membranous band extending from optic nerve head to temporal periphery with subretinal exudation and exudative retinal detachment temporally.

Treatment

Patient was started on oral steroids and planned for surgery. Vitrectomy with membrane peeling was done. Silicone oil was injected when break occurred while removing adherent membrane. Histopathological analysis of the membrane showed fibrous tissue with chronic inflammatory cells. No Toxocara parasite was seen.

Related reports

Ocular Toxocariasis usually occurs in young healthy children. It is usually limited to one eye and infected by one larva (Schlaegel, 1978). There are few clinical reports of retinal lesions in adults due to Toxocara infection. Larva is rarely identified from the lesions.

Peer review

This manuscript entitled "Multifocal Granulomata in Presumed Toxocara Canis Infection in Adult" to report a 45 years old case with fibrous membranous band extending from optic disc to temporal periphery with subretinal exudation and exudative retinal detachment temporally. A positive IgE titer of Toxocara was also found in AC tapping. This is an interesting paper and well written.

REFERENCES

1 **Pivetti-Pezzi P**. Ocular toxocariasis. *Int J Med Sci* 2009; **6**: 129-130 [PMID: 19319231 DOI: 10.7150/ijms.6.129]

2 **Nussenblatt RB.** Toxocara canis. In: Nussenblatt R.B., Whitcup S, editors. Uveitis: Fundamentals and clinical practice. Philadelphia: Mosby, 2004: 244-249

3 **de Visser L**, Rothova A, de Boer JH, van Loon AM, Kerkhoff FT, Canninga-van Dijk MR, Weersink AY, de Groot-Mijnes JD. Diagnosis of ocular toxocariasis by establishing intraocular antibody production. *Am J Ophthalmol* 2008; **145**: 369-374 [PMID: 18061138 DOI: 10.1016/j.ajo.2007.09.020]

4 **Schlaegel TF Jr,** Knox DL. Uveitis and Parasitosis. In: Duane TD, editor. *Clinical Ophthalmology* 1987; **4**: 10-14

5 **Park SP**, Park I, Park HY, Lee SU, Huh S, Magnaval JF. Five cases of ocular toxocariasis confirmed by serology. *Korean J Parasitol* 2000; **38**: 267-273 [PMID: 11138321 DOI: 10.3347/kjp.2000.38.4.267]

6 **Stewart JM**, Cubillan LD, Cunningham ET. Prevalence, clinical features, and causes of vision loss among patients with ocular toxocariasis. *Retina* 2005; **25**: 1005-1013 [PMID: 16340531 DOI: 10.1097/00006982-200512000-00009]

7 **Werner JC**, Ross RD, Green WR, Watts JC. Pars plana vitrectomy and subretinal surgery for ocular toxocariasis. *Arch Ophthalmol* 1999; **117**: 532-534 [PMID: 10206586 DOI: 10.1001/archopht.117.4.532]

8 **Amin HI**, McDonald HR, Han DP, Jaffe GJ, Johnson MW, Lewis H, Lopez PF, Mieler WF, Neuwirth J, Sternberg P, Werner JC, Ai E, Johnson RN. Vitrectomy update for macular traction in ocular toxocariasis. *Retina* 2000; **20**: 80-85 [PMID: 10696753 DOI: 10.1097/00006982-200001000-00015]

P- Reviewers: Jhanji V, Inan UU, Shih YF **S- Editor:** Song XX
L- Editor: A **E- Editor:** Lu YJ

World Journal of Ophthalmology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
www.wjgnet.com

World J Ophthalmol 2013 November 12; 3(4): I-V
ISSN 2218-6239 (online)

INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Ophthalmology (*World J Ophthalmol*, *WJO*, online ISSN 2218-6239, DOI: 10.5318) is a peer-reviewed open access (OA) academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

Aim and scope

WJO covers topics concerning optometry, ocular fundus diseases, cataract, glaucoma, keratopathy, ocular trauma, strabismus, and pediatric ocular diseases, blindness prevention, diagnostic imaging, evidence-based medicine, epidemiology and nursing. The current columns of *WJO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of ophthalmological diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

WJO is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 OA clinical medical journals, including 41 in English, has a total of 15 471 editorial borad members or peer reivewers, and is a world first-class publisher.

Columns

The columns in the issues of *WJO* will include: (1) Editorial: The editorial board members are invited to make comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Diagnostic Advances: The editorial board members are invited to write high-quality diagnostic advances in their field to improve the diagnostic skills of readers. The topic covers general clinical diagnosis, differential diagnosis, pathological diagnosis, laboratory diagnosis, imaging diagnosis, endoscopic diagnosis, biotechnological diagnosis, functional diagnosis, and physical diagnosis; (4) Therapeutics Advances: The editorial board members are invited to write high-quality therapeutic advances in their field to help improve the therapeutic skills of readers. The topic covers medication therapy, psychotherapy, physical therapy, replacement therapy, interventional therapy, minimally invasive therapy, endoscopic therapy, transplantation therapy, and surgical therapy; (5) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented (including authors, article title, journal name, year, volume, and inclusive page numbers; (6) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research of molecular biology, genomics, and related cutting-edge technologies to provide readers with the latest knowledge and help improve their diagnostic and therapeutic skills; (7) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (8) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic to help improve the diagnostic and therapeutic skills of readers; (9) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (10) Clinical Case Conference or Clinicopathological Conference: The editorial board members are invited to contribute high-quality clinical case conference; (11) Original Articles: To report innovative and original findings in ophthalmology; (12) Brief Articles: To briefly report the novel and innovative findings in ophthalmology; (13) Meta-Analysis: To evaluate the clinical effectiveness in ophthalmology by using data from two or more randomised control trials; (14) Case Report: To report a rare or typical case; (15) Letters to the Editor: To discuss and make reply to the contributions published in *WJO*, or to introduce and comment on a controversial issue of general interest; (16) Book Reviews: To introduce and comment on quality monographs of ophthalmology; and (17) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

Name of journal

World Journal of Ophthalmology

ISSN

ISSN 2218-6239 (online)

Launch date

December 30, 2011

Frequency

Quarterly

Instructions to authors
Full instructions are available online at http://www.wjgnet.com/2218-6239/g_info_20100722180051.htm.

Indexed and Abstracted in
Digital Object Identifier.

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing
Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement
In the interests of transparency and to help reviewers assess any potential bias, *WJO* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent
Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights
When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the

case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/esps/. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2218-6239/g_info_20100722180051.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to bpgoffie@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, *e.g.*, Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, *e.g.*, Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision on acceptance is made only when at least two experts recommend publication of an article. All peer-reviewers are acknowledged on Express Submission and Peer-review System website.

Abstract

There are unstructured abstracts (no less than 200 words) and structured abstracts. The specific requirements for structured abstracts are as follows:

An informative, structured abstract should accompany each manuscript. Abstracts of original contributions should be structured into the following sections: AIM (no more than 20 words; Only the purpose of the study should be included. Please write the Aim in the form of "To investigate/study/…"), METHODS (no less than 140 words for Original Articles; and no less than 80 words for Brief Articles), RESULTS (no less than 150 words for Original Articles and no less than 120 words for Brief Articles; You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, *e.g.*, 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$), and CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Core tip

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P <$

0.05, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of P values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, *e.g.*, PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2218-6239/g_info_20100724174652.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

All types of articles' writing style and requirement will be found in the link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

RESUBMISSION OF THE REVISED MANUSCRIPTS

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade A certificate (for non-native speakers of English), should be submitted to the online system *via* the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2218-6239/g_info_20100724174548.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2218-6239/g_info_20100724174456.htm.

Proof of financial support

For papers supported by a foundation, authors should provide a copy of the approval document and serial number of the foundation.

STATEMENT ABOUT ANONYMOUS PUBLICATION OF THE PEER REVIEWERS' COMMENTS

In order to increase the quality of peer review, push authors to carefully revise their manuscripts based on the peer reviewers' comments, and promote academic interactions among peer reviewers, authors and readers, we decide to anonymously publish the reviewers' comments and author's responses at the same time the manuscript is published online.

PUBLICATION FEE

WJO is an international, peer-reviewed, OA online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium and format, provided the original work is properly cited. The use is non-commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. All invited articles are published free of charge.

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza, 315-321 Lockhart Road,
Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com