

Title: Retinal Nerve Fiber Layer Thickness in Primary Open Angle Glaucoma and Primary Angle Closure Glaucoma.

Country: Malaysia

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Introduction:

Systemic diseases such as hypertension and diabetes mellitus are popularly identified as chronic disease. However, little is known about chronic diseases affecting the eye. Glaucoma is a chronic, irreversible neurodegenerative disease affecting the optic nerve that is characterized by specific pattern of visual fields (VF) defect. Progressive visual field defect usually affects the peripheral vision and gradually constricting the visual field causing 'tunnel' vision. The constricted field causes limited daily activities such as reading, driving and even mobility in the patient's own home. It is also reported to cause frequent fall among elderly (Haymes, Leblanc, Nicoleta, Chiasson, & Chahnan, 2007). Early diagnosis of glaucoma will improve quality of life among elderly.

Glaucoma is the second leading cause of blindness in the world after cataract (Quigley & Broman, 2006; Thylefors & Negrel, 1994). The prevalence of glaucoma is expected to increase every year and lead to a substantial public health challenge worldwide (Pan & Varma, 2011). Age is the most important risk factor for primary glaucoma. Primary glaucoma is further divided into open angle and closed angle glaucoma based on the angle configuration. The risk of glaucoma increases with age in both primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG). As the health services improved in most part of the world, the life span is increased exponentially. Thus, it is not surprising that both POAG and PACG prevalence will be increased.

Asians represented approximately half of those with glaucoma and nearly 87% of those with ACG in 2010 (Quigley & Broman, 2006). It was estimated that 60.5 million of the world population will be affected by open angle glaucoma (OAG) and angle closure glaucoma (ACG) in 2010, and further increase to 79.6 million people by 2020 (Quigley & Broman, 2006). Out of this, 4.5 million people with OAG and 3.9 million people with ACG is estimated to develop bilateral blindness and, further rise up to 5.9 million and 5.3 million people in 2020, respectively (Quigley & Broman, 2006). PACG is known to cause more blindness than POAG. According to a study by (Reddy, Tajunisah, Low, & Karmila, 2008) glaucoma was the second most common eye disease in urban population in Malaysia. Based on the results from the National Eye Survey 1996, glaucoma was the fifth major cause of blindness and low vision in Malaysia (Zainal et al., 2002). It also showed that glaucoma was the third most common cause of irreversible and progressive visual impairment in Malaysia.

Diagnosis of glaucoma remained an elusive issue. There is no real consensus in definition of glaucoma. Late presentation in POAG and PACG is common (Gogate, Deshpande, Chelkerkar, Deshpande, & Deshpande, 2011). This is mainly due to lack of symptoms especially in POAG. Glaucoma is best known as the 'thief of sight'. Early diagnosis is important to prevent blindness.

Retinal nerve fiber layer (RNFL) thinning is a hallmark of glaucomatous optic neuropathy. RNFL thinning is difficult to detect during clinical examination with funduscopy or slit-lamp fundus biomicroscopy. With the advancement of technology, imaging of optic nerve head is possible with high accuracy almost similar to surgical dissection of the optic nerve head. Cross-sectional imaging and measurement of the RNFL using Optical Coherence Tomography (OCT) is reliable and shows high accuracy of structural changes of the optic nerve head (Budenz, Fredette, Feuer, & Anderson, 2008; Leung et al., 2009; Paunescu et al., 2004). Structural defect is believed to occur prior to functional defect. Functional defect is detected by visual field analysis. Identification of structural defect is important to prevent further functional defect. Appropriate management at the early stage of glaucoma may prevent further progression of the disease. Detection of early structural damage at the early stage of the disease may improve quality of life of glaucoma patient.

In the present study, our main objective was to determine the difference of mean RNFL thickness between POAG and PACG. We also aimed to determine the difference between the two main types of glaucoma according to severity of the disease.

Material and Methods:

A cross sectional study was conducted involving 80 glaucoma patients; 49 POAG and 31 PACG patients who attended the ophthalmic clinic of Hospital Universiti Sains Malaysia. Ethical approval was obtained from Ethical Research Board of School of Medical Sciences, USM. The study was conducted between September 2012 and October 2013. Patients were selected based on strict inclusion and exclusion criteria. If both eyes fulfilled the selection criteria, only right eye was selected.

Recruitment:

The definition of POAG or PACG was based on ISGEO classification (Foster, Buhrmann, Quigley, & Johnson, 2002). Informed consent was obtained from the patients during the recruitment process. The selection was based on the inclusion and exclusion criteria as below:

Inclusion criteria:

Age >40 years old.

Confirmed cases of POAG and PACG.

Refractive error of spherical equivalent between -4 D and +4 D, astigmatism less than 4D

Clear ocular media.

Exclusion Criteria:

Secondary glaucoma (e.g. traumatic glaucoma, uveitic glaucoma, neovascular glaucoma)

Glaucoma Suspect.

Unreliable and not reproducible visual field after third attempt.

Any other retina pathology of that may give risk to visual field defect (e.g. diabetic and hypertensive retinopathy, age related macular degeneration, retinal detachment (RD), retinitis pigmentosa)

History of ocular surgery including glaucoma surgery, vitrectomy, retinal detachment

Ocular examination:

A detailed ocular examination was conducted by trainee ophthalmologist and glaucoma consultant. Examination includes visual acuity using Snellen chart and thorough anterior segment slit-lamp examination, which include Goldmann Applanation Tonometry, gonioscopic evaluation and fundus examination. Any patient with media opacity that will affect the signal of image taken by OCT will be excluded. The severity of glaucoma was determined using Humphrey visual field analyzer using 24-2 SITA Standard program. A reliable consecutive visual field was used to determine the severity based on the Advanced Glaucoma Intervention Study (AGIS). A visual field test is considered reliable if fixation losses <20%, false positive error < 33%, and false negative error < 33%. A postgraduate student who has been trained in AGIS scoring was responsible in scoring the severity of glaucoma. A score of 1-5 was categorized as mild, 6-11 as moderate, 12-17 as severe and 18-20 as end-stage or advanced. The scoring was then re-evaluated by glaucoma consultant.

RNFL thickness evaluation

ONH parameters were evaluated using Cirrus-HD OCT. The machine was operated by trained technicians. If the OCT image was not good (low signal strength), eyes were dilated using phenylephrine eye-drops. ONH parameters were evaluated using Cirrus-HD. Only a good acceptable OCT imaging with a signal strength $\geq 4/10$ (Ha et al., 2012) and a well-centered optic nerve head was selected. Data regarding retinal nerve fiber layer thickness, rim area, disc area, vertical cup disc ratio and cup volume were recorded.

Statistics:

The statistical analysis was performed using the SPSS version 20.0 software. All the parameters were analyzed using Pearson chi-square and Fischer exact test for categorical data. The RNFL thickness and ONH parameters between POAG and PACG were determined using independent t-tests. A *p*-value < 0.05 was deemed statistically significant.

Results:

A total of 49 POAG and 31 PACG were recruited in this study. 71 (88.8%) were Malays. There was significant difference in sex distribution between POAG and PACG ($p=0.002$). There was female preponderance among PACG patients (Table 1). Most of the glaucoma patients were retiree. Majority have received some form of formal education (Table 1). Systemic hypertension is the most common systemic comorbidities in patients with POAG and PACG. There were significantly more patients with systemic hypertension in POAG compared to PACG (table 2).

Slightly more than half (58.1%) of PACG patient presented with history of acute attack. PACG patients have higher IOP and more advanced glaucoma compared to POAG (table 3.1). In spite of the advanced stage of glaucoma, majority still have good visual acuity (6/12 or better) (table 3.1).

The evaluation of ONH parameters and RNFL thickness is illustrated in figure 1. In spite of PACG was more severe compared to POAG, there was no significant difference in RNFL thickness, vertical cup to disc ratio, rim area and cup volume (table 4).

However, based on AGIS scoring, there was significant difference of vertical cup disc ratio, rim area and cup area between POAG and PACG at mild stage of the disease. Mild stage of PACG demonstrated small cup volume but bigger rim area compared to POAG. Mean RNFL thickness did not show statistical significant difference between this two type of glaucoma. There was statistical difference in ONH parameters and RNFL thickness in other stages of glaucoma.

TABLE 1: Demographic Characteristics

Demographic characteristics	POAG N = 49	PACG N = 31	<i>p</i> -value
Age			
Mean	67.1	65.0	0.326 [*]
SD	9.4	8.9	
Sex, n (%)			
Male	35 (71.4)	12 (38.7)	0.002 ^{**} (<i>p</i> < 0.05)
Female	14 (28.6)	19 (61.3)	
Race, n (%)			
Malay	46 (93.9)	25 (80.6)	0.082 ^{***}
Chinese	3 (6.1)	6 (19.4)	
Education, n (%)			
Formal Schooling	42 (85.7)	23 (74.2)	0.170 ^{**}
No Formal schooling	7 (14.3)	8 (25.8)	
Profession, n (%)			
Retired	34 (69.4)	20 (64.5)	0.872
House wife	7 (14.3)	7 (22.6)	
Odd job	2 (4.1)	1 (3.2)	
Supporting staff	1 (2.0)	1 (3.2)	
Professional	5 (10.2)	2 (6.5)	
<i>p</i> < 0.05 based on * independent <i>t</i> -test, ** Pearson chi-square test and *** Fischer exact test POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma.			

TABLE 2: Systemic illness between POAG and PACG

Demographic characteristics	POAG	PACG	<i>p</i> -value
Systemic illness, n (%)			
Hypertension	36 (70.6)	13 (41.9)	0.010**
Hyperlipidemia	20 (39.2)	10 (32.3)	0.526**
Diabetes mellitus	21 (41.2)	9 (29.0)	0.268**
Cardiovascular disease	8 (15.7)	6 (19.4)	0.669**
Cerebrovascular accident	5 (9.8)	0 (0.0)	0.072***
<i>p</i> < 0.05 based on ** Pearson chi-square test and *** Fischer exact test POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma.			

TABLE 3.1: Ocular parameters

Ocular parameters	POAG N = 49	PACG N = 31
Visual acuity, n (%)		
6/6	4 (8.2)	6 (19.4)
6/7.5 to 6/12	37 (75.5)	19 (61.3)
6/18 to 6/24	8 (16.3)	3 (9.7)
6/36 to 6/60	0 (0.0)	1 (3.2)
CF	0 (0.0)	2 (6.5)
Lens status, n (%)		
Clear	10 (20.4)	8 (25.8)
Immature cataract	32 (65.3)	18 (58.1)
Pseudophakia	7 (14.3)	4 (12.9)
Cataractous	0 (0.0)	1 (3.2)
AGIS score, n (%)		
Mild	22 (44.9)	9 (29.0)
Moderate	16 (32.7)	5 (16.1)
Severe	4 (8.2)	3 (9.7)
End-stage	7 (14.3)	14 (45.2)
IOP		
Mean	15.4	17.3
SD	3.20	6.30
VCDR		
Mean	0.79	0.79
SD	0.10	0.10
POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; CF, counting finger; AGIS, advanced glaucoma intervention study; IOP, intraocular pressure; VCDR, vertical cup disc ratio.		

TABLE 3.2: Ocular parameters

Ocular parameters	POAG	PACG	p-value
Visual field mean deviation (dB)			
Mean	-10.4	-14.1	0.091
SD	7.08	12.37	
Visual field pattern standard deviation (dB)			
Mean	6.5	7.1	0.565
SD	3.12	4.14	
All p-value based on independent t-test			
POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma.			

TABLE 4: ONH parameters and RNFL thickness

OCT findings	POAG	PACG	p-value
RNFL Thickness (μm)	66.3	71.3	0.200
VCDR	0.81	0.78	0.077
Rim Area (mm ²)	0.70	0.78	0.300
Cup Volume (mm ³)	0.709	0.674	0.714
P<0.05, independent t-test			
OCT, Optical Coherence Tomography; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; RNFL, retinal nerve fiber layer; VCDR, vertical cup disc ratio.			

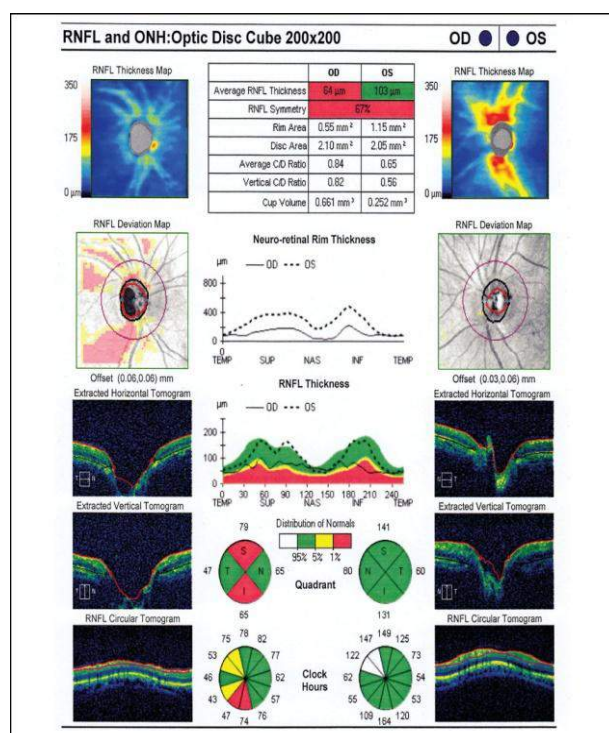


Figure 1: show the example of OCT result

TABLE 5: Comparison of ONH parameters between POAG and PACG according to severity

ONH parameters	Severity											
	Mild N = 31			Moderate N = 21			Severe N = 7			End-stage N = 21		
	POAG n = 22	PACG n = 9	p-value	POAG n = 16	PACG n = 5	p-value	POAG n = 4	PACG n = 3	p-value	POAG n = 7	PACG n = 14	p-value
RNFL (μ m)	69.77	79.11	0.186	67.44	80.40	0.188	56.25	66.33	0.188	58.71	63.69	0.434
VCDR	0.79	0.70	0.001*	0.81	0.72	0.106	0.82	0.74	0.313	0.85	0.84	0.762
Rim Area (mm ²)	0.73	0.96	0.024*	0.77	0.97	0.158	0.60	0.89	0.366	0.55	0.58	0.877
Cup Volume (mm ³)	0.751	0.452	0.012*	0.642	0.526	0.334	0.617	0.331	0.217	0.782	0.944	0.572

* significant ($p < 0.05$) based on independent t-test
 ONH, optic nerve head; OCT, Optical Coherence Tomography; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; RNFL, retinal nerve fiber layer; VCDR, vertical cup disc ratio.

DISCUSSION

Detection of glaucoma at the early stage of the disease is important to strategizing effective management and prevention of blindness. Ability to arrest progression at the early stage of the disease may improve the quality of life of glaucoma patients. There was moderate correlation between severity of the disease and quality of life of the affected patients in Malaysia (Maharajah, Tet, Yaacob, Tajudin, & Foster, 2008). However, public screening is not effective and expensive (Burr et al., 2007; Hollo, Kothiy, Geczy, & Vargha, 2010).

Structural changes in glaucoma precede functional changes. The nerve fiber layer (NFL) can be detected clinically in most individuals, and is best appreciated using the red-free setting on the ophthalmoscope or slit-lamp. The normal NFL can be visualized clinically, photographically or with optic nerve head analyzers such as optical coherence tomography (OCT). OCT is a noninvasive and non-contact modality with good reproducibility (Wu, de Boer, & Chen, 2011). It can be used to obtain structural changes in retina and potential equipment for early diagnosis of glaucoma and monitoring its progression (Hee et al., 1995; Schuman et al., 2003).

In this present study, Optical Coherence Tomography (OCT) was used to identify structural changes at ONH. There was no statistical significant difference of mean RNFL thickness between POAG and PACG. POAG and PACG are the most common type of glaucoma. Although the prevalence of PACG is higher in Asia compared to Caucasian but POAG remain the most prevalent type of glaucoma. PACG in Asians behaves differently compared to Caucasians (Ang, 2008). In Asian population, PACG behaves similarly to POAG with low reported cases of acute presentation of angle closure (APAC). APAC is characterized by sudden raised of IOP that causes pain and sudden reduction of vision. Those with APAC usually presented earlier rather than those without APAC. Similarly, in this present study only 41.9 % demonstrated history of APAC. Perhaps, this contributes to late presentation and higher incidence of blindness in Asians.

On contrary, (Manassakorn & Aupapong, 2011) reported thicker RNFL in PACG compared to POAG. Our finding may be affected by smaller number of subject of PACG. Comparatively, there was slightly more patients with advanced or end stage glaucoma in PACG patients. In addition, there were significantly more women among PACG patients. This is of no surprise as women were at more risk to develop PACG (Wong, Foster, Seah, & Chew, 2000); (Boland et al., 2008; Fortune, Burgoyne, Cull, Reynaud, & Wang, 2013). It was a well-documented fact that women are more likely to be diagnosed with PACG (Foster et al., 2002). Perhaps, women have thicker RNFL as their baseline compared to men.

There was statistical significant difference of rim area, cup volume and vertical cup to disc ratio between PACG and POAG at the mild stage of glaucoma. As expected due to the overcrowding, RNFL was thicker in PACG patients compared to POAG. Although this is not statistically significant difference. In general, although not statistically significant difference, similar finding was observed in moderate and severe glaucoma. Similar observation was reported by (Sihota, Sony, Gupta, Dada, & Singh, 2005) in Indian population.

At the advanced or end stage of glaucoma, changes at ONH are similar in any type of glaucoma. Early detection of ONH is important in strategizing more effective management and prevention of blindness. Since PACG cause more blindness, early diagnosis is extremely important. Awareness of the disease is important for early diagnosis too. Undergraduate students are considered as primary eye care provider. As primary eye care provider, it is important for us to help in improving awareness in general public. Community engagement project is more effective in providing awareness among the local population. Our sensitivity to their culture and belief is the key to successful preventive measure. High risk patients such as those with family history of glaucoma should be encouraged for eye screening examination. Undergraduate medical students should take part during the World Glaucoma Week. During that week, various effective activities should be designed to improve awareness in general population and authorities.

The local government should also be aware of this blinding problem. Adequate amount of budget should be allocated for better facilities in the hospital especially in providing imaging technology in government hospital and training adequate ophthalmologist. In Malaysia, especially in rural area, the ophthalmologist to population ratio is far from adequate. While in the urban area, it is more than adequate. This imbalance should be addressed as our population is ageing faster than expected.

Conclusion

Detection of early structural changes in glaucoma patients is important to strategizing more effective management. OCT is good tool to evaluate the early changes of optic nerve head. Identifying early structural changes can prevent further functional changes in glaucoma patients.

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SCIENTIFIC PAPER COMPETITION – MONGOLIA

Liver cancer in Mongolia. A systematic review of current situation and its management.

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Abstract

Background

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Worldwide, HCC is the sixth most common cancer by incidence and responsible for the third highest mortality among all cancers. Most cases are reported in developing countries where chronic viral hepatitis B and C are endemic, such as in sub-Saharan Africa and East Asia. Mongolia has the highest incidence of HCC worldwide. In 2011, the age-standardized incidence of HCC was 122.4 in men and 79.6 in women per 100,000, according to National Cancer Center (NCC) statistics. Chronic HBV and HCV infection, as well as alcoholism, are endemic risk factors of cirrhosis and subsequent HCC in Mongolia.

Material and methods

The search plan for this systematic review was focused on the PubMed/Medline index, as well as material indexed by the Cochrane Collaboration. There were no exact exclusion criteria, except that literature published before the year 2000 was not considered. Cancer statistics for Mongolia were mainly gathered and analyzed from the NCC's Statistical and Information department. Some unpublished studies were provided by the Ministry of Health and were included with permission.

Results

Our review indicates that throughout the coming decade, liver cancer will remain the most incident cancer in Mongolia and continue to cause the most cancer-related mortality. Due to the national HBV vaccination campaign, vertical transmission and infection of HBV in children has been decreasing since 1991. However, HCV infection remains an endemic predisposing risk factor for HCC. Diagnostic and therapeutic capacities are highly limited and curative surgery accounts for a very low proportion of therapies due to late-stage diagnoses.

Conclusion

In Mongolia, chronic liver diseases constitute a public health emergency. Improved screening and periodic nationwide assessments of liver cancer will be important aspects of management of HCC in our country's future. As the major predisposing factor of cirrhosis and liver cancer, treatment of chronic viral hepatitis should be a top priority.

Liver cancer in Mongolia. A systematic review of current situation and its management.

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Introduction

Worldwide, liver cancer is the fifth most incident cancer in men (522,000 cases, 7.9% of total cancer cases in men) and the seventh most incident in women (226,000 cases, 6.5% of total). Most of the burden of liver cancer is borne by developing countries, where almost 85% of cases occur. The majority of cases occur in men, such that the male:female incidence ratio is 2.4.(GLOBACON 2008) GLOBACON 2008 indicates that liver cancer is the third common cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) is the most common histologic type of primary liver cancer globally. (Simon & Robinson, 2008)

Most cases of HCC occur in Asia, where several countries, particularly in East Asia, display an extremely high incidence (over 20 cases/100 000 population). Age-standardized incidence is estimated at 99 per 100 000 persons in Mongolia, 49 per 100 000 in Korea, 35 per 100 000 in China, and 29 per 100 000 in Japan. (Simon & Robinson, 2008) It is estimated that 1 of every 10 deaths in Mongolia is due to HCC or its frequent precursor, cirrhosis. (Alcorn, 2011) Mongolia has the highest incidence and mortality of HCC worldwide, and 6 times the global mean incidence. (Alcorn, 2011; Amarsanaa et al., 2012)

The National Cancer Center is the Mongolia's only third level care hospital for HCC diagnosis, treatment and palliation, and is located in the capital city of Ulaanbaatar. Mongolia's sparsely spread population and the long distances separating primary caregivers makes early detection and treatment very difficult, contributing to high er mortality.

Incidence and Death rate

According to data from the World Health Organization, in 2008 the age-standardized mortality rate of cancer in Mongolia was among the highest in the world, at 260 males and 166 female deaths per 100 000. Over the past decade, cancers were the second most common cause of death in Mongolia. The Department of Cancer Registry and Information of the National Cancer Center provides the most accurate cancer data and statistical analysis in the country. Among all cancers in Mongolia, primary liver cancer has been the most incident and prevalent since 1987, and has risen significantly since 1973. (Tuvshingerel et al., 2010) Linear regression indicates a statistically significant rise in the incidence rate of liver cancer from 1991 to 2011, increased by a factor of 1.37 in males and 1.59 in females according to National Cancer Center statistics. Unsurprisingly, the total incidence of all types of cancers has also been increasing significantly in both sexes. It is estimated that cancer incidence in our country will be relatively stable for the next decade, and that liver cancer will remain the leading cancer. (Database of National Cancer Center of Mongolia) Between 2003 and 2007, total of 17271 new cancer cases in Mongolia were recorded by the National Cancer Registry. Of these cases, primary liver cancer was the most common cancer type both in men (accounting for 41.3% of all cancer incidence in men) and women (accounting for 32.5% of all cancer incidence in women). (Database of WHO) It is not clear why men have a higher incidence of primary liver. The National Cancer Center's Registry and Statistical department has liver cancer incidence data collected as recently as 2011: 122.4 men and 76.1 women per hundred thousand, as expressed by age-standardized rates. Follow-up cancer care is poorly developed in Mongolia, and published five-year survival data does not exist. However, outcomes are generally

expected to be very poor to be poor. A study of Jazag et al approximated HCC survival rates in Mongolia at 21-24% for 1-year survival, 10-11% for 3-year survival, and 6-8% for 5 year survival.

Chronic viral hepatitis as a primary risk factor

In most patients, HCC is preceded by cirrhosis of the liver and, as expected, risk factors for cirrhosis have been identified as key risk factors for HCC as well. (Donoghue et al., 2011) Both HBV and HCV remain the leading risk factors of liver cirrhosis and HCC. (Alejandro.F et al., 2012) Mechanisms of molecular and genetic pathogenesis of HCC are still poorly understood. A seminar review article by Alejandro.F et al. (2012) noted that p53 mutation is present in 25-40 percent of HCC patients and a β catenin mutation (CTNNB1) occurs in 25% of HCV-related hepatocellular carcinomas.

There exists one previous nationwide Hepatitis C virus (HCV) prevalence study conducted by Baatarxuu.O et al. published in 2008. This was a nationwide, population-based cross-sectional study using two-stage cluster random sampling. In this study, the investigators enrolled 1512 apparently healthy individuals both from urban and rural areas, as well as a high-risk population of 96 nurses. Major findings included an overall prevalence of anti-HCV and HCV RNA among study subjects of 15.6% (236/1512) and 11.0% (167/1512), respectively. Among 167 HCV RNA-positive samples, 165 (98.8%) were classified as genotype 1b and the remaining as genotype 2a. History of dental care, surgery and tattooing were identified as significant risk factors for hepatitis C virus infection.

It is known that between the 1960s and early 1990s the increase in prevalence of HCV infection was heavily influenced by repeated use of un-sanitized syringes, as well as traditional blood-letting therapies, blood transfusions performed without pre-screening for anti-HCV RNA, and other risky practices. (Ebright.JR et al., 2003) According to National Cancer Center statistics, hepatocellular carcinoma incidence is highest in Mongolians aged 40-60 years, which corresponds to the natural history of endemically transmission of HBV and HCV during 70s to 80s. In a study by Oyusuren.T et al, 38.9 percent of hepatocellular carcinoma patients were mono-infected with HCV, 5.8 percent were co-infected with HBV and HCV, and 18.5 percent were infected by triple-infected with HBV, HCV and HDV. Study populations were selected from third level national hospitals and NCC. Prevalence of multiple infections was even higher in non-HCC cirrhotic patients.

The current gold standard of treatment for chronic hepatitis C is pegylated interferon based therapies. Administered with Ribavirin, sustained virologic response is observed in approximately 40-50% of patients with HCV genotype 1 infection. (Hugo R.R, 2011) Boceprevir and Telaprevir are new-era drugs that have been approved recently by the FDA, but it is still advised that these be administered concurrently with pegylated interferon therapy and Ribavirin. (Noura M.D & Donald M.J., 2013) Sofosbuvir is another recently developed oral drug which has produced sustained virologic response in 90% of HCV genotype 1 and 4 cases when administered with peg-interferon therapy and Ribavirin. (Eric & Aless M.S, 2013) However, interferon and Ribavirin treatment is expensive; only a small proportion of chronically-infected persons are able to afford such treatment in our country. In estimation of Jazag et al, 6.34 billion US\$ is required for pegylated interferon for every HCV infected population.(2012)As the HCV epidemic continues to threaten Mongolian public health, the government should be more concerned about covering at least some portion of HCV interferon-based therapy as part of the national health insurance system, in order to limit the prevalence of cirrhosis and HCC.

Hepatitis B infection is another highly prevalent hepatitis infection in Mongolia and Asia.(WHO data; Katherine A.M & London W.T, 2011) More than 77% of Mongolians are estimated to have been infected with hepatitis B virus (HBV) at some time in their life, and between 10% and 22% of the general population is chronically infected with the virus.(Database of WHO) In recent years there have been no nationally representative prevalence studies of HBV infection in Mongolia. In 2005, Tsatsralt-Od.B et al published a study of viral hepatitis B, C and Delta prevalence in blood donors, indicating that approximately 10 percent of first-time donors were chronically infected with chronic HBV. Collected medical histories of NCC patients appearing between 2000 and 2009 indicated that 21% were co-infected with HBV and HCV. HBV infection was considered in presence of HBsAg, and anti-HCV for the HCV. (Tsatsralt-Od.B et al., 2005) Health-care workers (HCWs) are known to be at increased risk of hepatitis infection due to occupational exposure to blood and other body fluids by injuries from contaminated sharps. However, there is limited data on the burden of sharps injuries among HCWs in Mongolia. In a study of Khosbayar.T and Otgonbayar.B in 2010 (unpublished study of Ministry of Health and WHO representative office), the prevalence of anti-HBc, anti-HBs, HBsAg and HBeAg seropositivity were determined to be 83.3%, 36.4%, 9.6%, 0.3%, respectively in a total of 354 serum samples collected from HCWs. Twenty four (6.8%) samples of the 354 collected tested positive for anti-HDV. The prevalence of anti-HCV was 20.1% (71/354).

Upon introducing HBV vaccination for infants in 1991, the number of cases of acute viral hepatitis in Mongolia decreased dramatically from 68 cases per 10 000 in 1990 to 30 cases per 10 000 in 1992. (Oyun.M, 2010, unpublished study) The first nationwide survey of HBV infection assessed a total of 1145 Mongolian children aged 7-12 years, between 2004 and 2007, in which the overall prevalence of HBsAg and anti-HBc was observed to be 5.2% and 15.6% respectively. (Davaalkham et al, 2007) In 2011, findings from a second nationwide survey conducted between 2009 and 2010 were published. This study enrolled 5894 children aged 4-5 years and found that an HBsAg prevalence of 0.53 and a prevalence of full vaccination of 82%. (Database of WHO Representative office Mongolia) According to unpublished data collected by the Mongolian Field Epidemiology Program, current HBV vaccination coverage for infants of Ulaanbaatar is 89% (CI 85.8-92.3). (23) The Western Pacific Region's Representative office of WHO has claimed that Mongolia has reached the regional goal of HBV vaccination to reduce the seroprevalence of HBV to 2% in children based on two nationwide surveys. (Database of WHO Representative office Mongolia)

Other risk factors

Alcoholism is another well-known predictor for liver cancer around the world. The association between alcohol consumption and liver cancer is mostly attributed to alcohol's effect on hastening the progression of cirrhosis in humans. (Simon & Robinson, 2008; Alcorn, 2011) In Mongolia, alcohol consumption has been confirmed as a major risk factor for chronic viral hepatitis and cirrhosis. (Alcorn, 2011; Amarsanaa et al, 2012) A lack of exact data for alcohol consumption in chronic liver disease patients makes it difficult to estimate the direct effect of alcohol consumption on liver disease outcomes in our country. WHO's 2008 statistics suggest that total adult (15+ years of age) consumption is 3.41 liters per capita of pure alcohol in both sexes and influencing moderate rate of consumption.

Obesity and Diabetes Mellitus(DM)

A meta-analysis of 21 prospective studies carried out by Yuqin Wang et al (2012) showed that body mass index was non-linearly associated with incidence of primary liver cancer worldwide. Specifically, a BMI of greater than 32kg/m² was found to be associated. Interestingly, HCV infection alone was strongly associated with HCC risk. This finding may suggest that the two risk factors, HCV and adiposity, could synergize to increase the risk of incident HCC. In a cross-sectional nationwide study by Otgontuya.D et al (2009) of 450 Mongolian subjects, obesity was found to be significantly higher in women (13.3%) than men (7.5%). Diabetes is known to be another strong risk factor for HCC even in non-HBV and HCV infected populations. Both for obesity and diabetes mellitus, nationwide data do not exist for Mongolia until recently. (Duuge.O et al., 2009)

Other important risk factors include mycotoxin named aflatoxin B1 exposure, poor diet regimens, genetic predispositions, and others. (Simon & Robinson, 2008; Alejandro.F et al, 2012)

Diagnostic capabilities

Alpha fetoprotein(AFP)

AFP is the most widely used tumor marker for detecting patients with HCC. AFP is a normal serum protein synthesized by fetal liver cells and yolk sac cells. The normal range for AFP is 10–20 mg/ml and a level >400 mg/ml is usually regarded as diagnostic of HCC. (Malati, 2007) Overall sensitivity of AFP for the detection of HCC is about 60%; two thirds of HCC tumors less than 4 cm in diameter are accompanied by AFP levels less than 200 mg/ml and up to 20% of tumors do not produce AFP, even when very large. A rising AFP over time, even in cases when the level does not reach 400 mg/ml, is almost always diagnostic of HCC. (Gupta, 2003)

In our country, AFP serum tests are routinely administered in both public clinical laboratories (such as at the NCC) and private ones. However, national health insurance covers only one AFP test, which is not satisfactory for testing time-trends of a patient's AFP level. Other highly sensitive and specific serum markers such as PIVKA-II, des-gamma carboxyprothrombin and AFP-L3 have not been introduced for HCC diagnosis in Mongolia.

Ultrasound (US)

Limitations in the sensitivity of AFP in surveillance of high-risk populations has led to the use of ultrasound as an additional method for the detection of HCC. (Sung et al, 2007) Ultrasound can detect large HCC tumors with high sensitivity and specificity, although it is less able to reliably identify smaller lesions, which are required if more effective personalized therapy is to be offered. (Dushyant.V et al., 2004) Combined use of ultrasound with AFP for surveillance increases detection percent and decreases false positivity. (Alejandro.F et al., 2012) The number of US machines in Mongolia is very limited, especially outside Ulaanbaatar, and the quality of US machines and examiners is generally unsatisfactory. (Baatarhuu.O, 2011) Ultrasound or CT-guided fine needle aspirational liver biopsy is a very sensitive and specific method for the diagnosis of HCC, although in Mongolia biopsy is rarely performed. Only an 60 annual instances of this test are estimated due to a lack of qualified professional and hospital capacity. (Baatarhuu.O, 2011)

Computed Tomography (CT) and Magnetic Resonance Scan (MRI)

In Mongolia, Radiographic examinations are diagnostically very important since liver biopsy tests are not routinely done. In a systematic review of Colli.A et al (2006), CT scan was more sensitive than US with less specificity than US. MRI had even greater sensitivity than US and CT scans however less specificity where found. (Colli.A) Only 2 CT machines are available in the country, which are located in NCC and in another state hospital and also their quality considerations were reported in Baatarhuu.O's study. (2011)

Treatment options

Surgical resection

Major hepatectomy (liver resection) and liver transplantation are the main treatment options for HCC. Until the present year, Cochrane's Reviews include no randomized clinical trials to support or refute the comparative effectiveness of surgical resection compared with liver transplantation for patients with hepatocellular carcinoma. (Taefi.A et al., 2013)

The Department of Hepatobiliary and Pancreatic Surgery of the NCC, which was established in 2008, provides surgical resection for patients referred from across Mongolia and remains the only hospital operating. In modern practice, patients with Child-Pugh score A or B are considered for resection is this standard of care for Mongolia as well as in other countries. (Sunduijav.R, 2012) Two surgical methods are used for major surgical resection: the conventional approach and the Glissonian pedicle approach. In Mongolia, Major hepatectomy accounts about 30% of all liver surgeries and minor hepatectomy accounts for 60–70%. Patients who underwent major liver resection using a Glissonian pedicle approach survived longer than those who received the conventional method. (Jazag et al, Baatarhuu.O, 2011) Due to the commonness of late diagnosis of liver cancers, surgical approaches are rarely recommended, such that only 16% of patients with HCC are considered eligible for major resection. (Jazag et al; Baatarhuu.O, 2011) Postoperative complications including liver failure occurred in 16 percent of cases. (32)

Liver transplantation was first introduced in Mongolia in 2009 at the National Central Hospital of Mongolia, but since then livers have only been transplanted from relatives of recipients due to legal conditions. It is estimated that living donor liver transplantation could be done for 500 patients annually at the National Central Hospital of Mongolia, but the current number of living donor liver transplantations is not adequate. Cadaveric organ transplantation is should be considered.

Radiofrequency Ablation (RFA) and Trans-arterial Chemo-Embolization (TACE)

Early stage treatments are limited in Mongolia. Less invasive treatments, mainly TACE and RFA, are performed for patients more commonly due to feasibility with late cancer stage. In two recent studies, TACE was performed predominantly in Baatarhuu.O et al and Jazag et al respectively, 44.2% and 27% of all patients who received treatment, while RFA was performed for 11.8% only. Lipiodol-based chemical agents such as doxorubicin (the most frequently used), 5-fluorouracil, and cisplatin are available in Mongolia. (Sunduijav.R, 2012) Cochrane Review that involved nine trials of 645 subjects, by Oliveri RS et al. indicates that survival is not significantly different between TACE and TAE groups compared with placebo or control. Number of statistical mistakes were reported in studies involved in this review. (Oliveri. RS, 2011)

Palliative care has been developing very fast in our country. The only remaining study of liver cancer patient palliation is Byambasuren Yo & Odontuya D.(2012) study in Mongolia. Epidural and Oral usage of morphine significantly reduced pain and increased quality of life in this study.

Prevention and Nationwide survey

The nationwide newborns' HBV vaccination campaign will play an important role in prevention of HCC in Mongolia's future, during which vertical transmission is more likely to produce chronic infection and complications. (Database of WHO Representative office Mongolia; Oyun.M, 2010) However, vaccination of HCV is still not available even outside of Mongolia.

Recently, two types of HCC risk prediction models have been published for use in the general public. One of these was proposed by Wen CP et al (2012), and involves using serum levels of transaminases. This may be a cost-effective method for implementation in a nationwide survey. Another risk prediction model was developed by Michikawa.T et al (2012), and involves a simple 10-year risk prediction scoring system for HCC. As for screening, Mongolia should initiate routine screening programs using ultrasound and serum α -fetoprotein. (Baatarxuu.O, 2011)

In conclusion, hepatocellular carcinoma constitutes a public health catastrophe in Mongolia, the country with the highest incidence of the disease worldwide. It is expected that HCC will remain the leading cause of cancer morbidity and mortality in Mongolia during the coming decade. Both the diagnostic and therapeutic capabilities of HCC are extremely limited in Mongolia, where their demand greatly exceeds their supply. A representative nationwide survey of HCC and implementation of antiviral eradication treatment for chronic viral hepatitis will be crucial for decreasing the incidence of HCC in the future.

Conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

Acknowledgements

We gratefully thank Professor Baatarxuu.O and Erdenebulgan.B of Health Sciences University of Mongolia for their professional advice, Drs. Ariuntuya.O for her assistance in finding important unpublished data, Sabri Bromage for kindly editing, and Tuvshingerel.S and Tsolmontuya.Ts from NCC of Mongolia for their support on statistical areas.

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