WESTERN PACIFIC REGION INDEX MEDICUS

MONGOLIAN JOURNAL OF HEALTH SCIENCES

VOLUME 5
ISUE 1
DECEMBER 2008

MONGOLIAN JOURNAL OF HEALTH SCIENCES

The **Mongolian Journal of Health Sciences was founded in 2003 to provide a means for the interchange of ideas among Mongolian medical professionals and foreign countries to advance the skill and knowledge of health** sciences, based on a peer **review process by the foremost** authorities **in all health sciences. The Mongolian Journal of Health Sciences will continue to** provide information for the standard for health care.

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Printed by "Erhes" Printing factory of the Health Sciences University of Mongolia

Volume 5 Number 1
Dec 2008
Indexed in Western Pacific Region Indicus Medicus (WPRIM), WHO

MONGOLIAN JOURNAL OF HEALTH SCIENCES

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Volume 5 Number 1
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MESSAGE FROM THE EDITOR-IN-CHIEF

Desr readers.

The beginning of a new year is both a time forward and for reflecting on past accomplishments. Each year in this space *e offer our heartfelt thanks to the volunteer peer viewers who help ensure the quality and integrity of the Mongo- ~«~ Journal of Health Sciences. We simply couldn't be successful in our jobs as editors withouttheir continued dedication JCC commitment to the scientific community.

This issue is dedicated to the hundreds of qualified medical professionals, academic staff, graduate students and scsefs. v.ho are loyal readers and contributors.

Mongolian Journal of Health Sciences was first published in 2003. It has been 66 years since the development of Vtrcgolian medicine has pursued the policy of modern scientific medical approach. Alongside with active development of sar-onal health sector, medical practitioners and specialists have duly invested in the establishment of scholarly research 2 s r with capacity to conduct studies at contemporary level in the area of medicine.

Since the victory of the democratic revolution and economic transition from a centrally planned to a free market scooom) in 1990, the trend, content and goal of medical research has changed to a new scientific perspectives as well as renarkable improvement of researchers' knowledge and capacity.

Many of young promising medical scientists are successfully working in the modern scientific laboratories and re-search institutes of Mongolia as well as those of developed countries. Their research results are sited and published at the rremaiionally recognized journals with high impact factor. Therefore, one of the goals of Mongolian Journal of Health Sciences is to disseminate and share our accumulated research achievements and experiences with international research cotieagues and scholars.

We are proud that Mongolian Journal of Health Sciences was successfully registered to the WPRIM opening a door jrocmous opportunities to introduce our journal to the Asian Pacific Region Countries' academic colleagues. We do hope !fez the publication of Mongolian Journal of Health Sciences will be a channel for future fruitful collaboration and lead _s to the new unexplored areas of research horizon.

All the best wishes to the dear readers of Mongolian Journal of Health Sciences!

Editor-in-Chief

REVIEW ARTICLE

Kawasaki Disease: Diagnosis, Treatment and Epidemiology

Davaalkham D,[1]* Baigalmaa D,[2] Nakamura Y [3]

ABSTRACT

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology affecting predominantly infants and toddlers. Approximately 85% of patients with Kawasaki disease are younger than 5 years old; patients aged less than 3 months or more than 5 years are encountered rarely and are at increased risk for coronary artery aneurysm formation. First described in Japan in l967 by Tomisaku Kawasaki, the disease is now known to occur in both endemic and community-wide epidemic forms in the Americas, Europe, and Asia in children of all races. Kawasaki disease is now the commonest cause of acquired heart disease in children in developed countries. It is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. The most important complication, coronary arteritis leading to formation of aneurysms, occurs in 20-30% of untreated patients. The increasing frequency of the disease as well as the deficiency of specific diagnostic means renders its diagnosis and treatment an area of intense investigation. Although an infectious agent is suspected, the cause remains unknown. The purpose of this review is to summarize all the known features of Kawasaki disease and also give an insight to the latest findings.

Key words: Mucocutaneous Lymph Node Syndrome, review, diagnosis, treatment, epidemiology

INTRODUCTION

Kawasaki disease (KD), or acute infantile febrile mucocutaneous lymph node syndrome, was originally described as a distinct clinical entity in Japanese children by Dr. Tomisaku Kawasaki in 1967[1], then in an English literature in 1974.[2] Since that time, KD has become the leading cause of acquired heart disease among children in developed countries. KD is an acute self-limited vasculitis of childhood that is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Although an infectious agent is suspected, the cause remains unknown. However, significant progress has been made toward understanding the natural history of the disease and therapeutic interventions have been developed that halt the immune-mediated destruction of the arterial wall.[3] Coronary artery aneurysms or ectasia develop in about 20% to 30% of untreated children and may lead to ischemic heart disease or sudden death.[4]

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Epidemiology

In the past, KD may have masqueraded as other illnesses, and old reports on infantile polyarteritis nodosa describe pathological findings that are identical to those of fatal KD.[5–6] Approximately 85% of patients with KD are younger than 5 years old; patients aged less than 3 months or more than 5 years are encountered rarely and are at increased risk for coronary artery aneurysm formation.[7]

Reported incidences of KD in different countries vary widely. KD is most common in Japan where the incidence rates are 10 times those in the United States, and 30 times that in the Unite Kingdom and Australia; worldwide the annual reported incidence varies from 3.4–174/100 000.The incidence of KD remains highest globally in Japan (174/100,000 population <5 years / year) and numbers continue to rise possibly as a result of increased awareness of the condition. The corresponding rate in Korea is estimated at 86.4/100 000 children less than 5 years old, while Taiwan is credited with a frequency of 66/100 000 referring to the same age group.[8,9] In the US, the incidence of KD has been estimated recently by using hospital discharge data. An estimated 4,248 hospitalizations associated with KD occurred in the United States in the year 2000, with a median age of 2 years. The highest incidence within the US is found in Hawaii, which reaches 17.1.[7] The annual occurrence rate per 100 000 children aged less than 5 years has doubled during the last decade in the United Kingdom and is reported to be 8.1, but 14.6 per 100 000 among Asian children with parents from the Indian subcontinent.[10]

Interestingly, the frequency among Japanese American children in Hawaii was higher than that among children of other races in the same state and when compared with children living in Japan. Beijing reported annual citywide incidence of 18.2 to 30.6 per 100 000,[11] and Hong Kong reported an annual incidence of 32 per 100 000. Australia had annual incidences of 3.7, and Sweden had 6.2 per 100 000.10,[12] The overall prevalence in the US is highest among Asian and Pacific Islanders, intermediate in non-Hispanic African-Americans, whereas the lowest was reported for Caucasians.[13]

There is a recurrence rate of 3.1% and the current fatality rate is 0.04% in Japan. Children aged 6 months to 5 years are most susceptible to KD, with peak incidence occurring in those aged 9-11 months.[14] Geographical outbreaks and seasonal variation in the numbers of cases have been reported.[15] Boys outnumbered girls by 3:2, and 85% of children were younger than age 5 years. In-hospital fatality rate was 0.17%. There is a peak occurrence in winter and spring months in Japan. Recent reports have emphasized the occurrence of KD in older children, who may have a higher prevalence of cardiovascular complications related to late diagnosis.[16–17]

Aetiology

The exact cause has not yet been established but there is considerable support for it is to be due to (an) infectious agent(s) causing disease among genetically vulnerable individuals.[18] The consensus is one or more widely distributed infectious agent(s) that evoke an abnormal immunological response in genetically susceptible individuals, lead to the characteristic clinical presentation of this disease. Moreover, a number of studies have linked KD with exposure to freshly cleaned carpets, habitation near a body of water, and humidifier use,[19] but descriptive epidemiologic data do not support such hypothesis.

Genetics

A genetic influence is suspected that increases the likelihood of acquiring KD and subsequently the formation of coronary artery lesions. The incidence rate varies between different ethnic populations, for instance Japanese immigrants have raised rates compared with the population of their new country, supporting the idea of a genetic influence[20]; siblings of index cases in Japan having an increased incidence of 8–9%.[21] In a study conducted in Japan using a nationwide survey, when compared with parents in the general population, the probability of a history of Kawasaki disease was significantly higher in those parents whose children suffered from the same disease. This suggests that, epidemiologically, a genetic predisposition to Kawasaki disease may be implicated in its occurrence.[22] It has also been suggested that genetic polymorphisms disseminated geographically amongst these populations may influence KD susceptibility, in particular polymorphisms in chemokine receptor genes, in the promoter of the CD14 gene and in some alleles of B and C in the HLA class I genes.[23,24] The CD40 ligand gene 11,and ITPKC genetic polymorphism 12 are thought to increase the tendency to develop coronary artery lesions. Because little evidence exists of person-to-person transmission, the hypothesis about genetic influence assumes that most infected children experience asymptomatic infection with only a small fraction developing overt clinical features of KD.[4]

In recent study report the importance of activated T cells in the pathogenesis of this vasculitis has been emphasized. The researchers identified a functional SNP (itpkc_3) in the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene on chromosome 19q13.2 that is significantly associated with KD susceptibility and also with an increased risk of coronary artery lesions in both Japanese and US children.[25]

Superantigens

The hypothesis that KD is related to a bacterial superantigenic toxin has been suggested because of the reported selective expansion of Vß2 and Vß8 T-cell receptor families, but this theory remains controversial.[26-29] Superantigens, such as those produced by Group A Streptococcus and toxic shock syndrome toxin-secreting and exfoliative toxin secreting Staphylococcus aureus are potent stimulators of T cells in the peripheral blood bearing specific Vβ receptors.[30]

Infectious agents

An infectious agent is strongly suspected in view of both clinical observations and a number of epidemiological features. Seasonality demonstrates a bimodal distribution, with peak incidence in late winter and early spring.[31] Thus it seems likely that KD is associated with some widely distributed infectious agent.[32] The coronavirus has been found in serological analysis of bodily secretions in up to 25% of cases of KD, although this is not felt to be the main causative factor.[33,34] It also is possible that KD results from an immunologic response that is triggered by any of several different microbial agents.[4]

Diagnosis

It has a number of classic clinical features required for diagnosis. The classic diagnosis of KD has been based on the presence of ≥5 days of fever and at least 4 of the 5 principal clinical features (Table 1). Typically, all of the clinical features are not present at a single point in time, and watchful waiting is sometimes necessary before a diagnosis can be made. Patients with fever for >5 days and >4 principal features can be diagnosed as having KD when coronary artery disease is detected by 2D echocardiography (2DE) or coronary angiography.

The fever typically is high spiking and remittent, with peak temperatures generally >39°C and in many cases >40°C. With appropriate therapy, the fever usually resolves within 2 days.

Table 1. Clinical and Laboratory Features of Kawasaki Disease

Epidemiological case definition (classic clinical criteria)*
Fever persisting at least 5 days†
Presence of at least 4 principal features:
Changes in extremities
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3 (desquamation)
Polymorphous exanthema
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
Cervical lymphadenopathy (≥1.5-cm diameter), usually unilateral
Other clinical and laboratory findings
Cardiovascular findings
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size noncoronary arteries
Raynaud's phenomenon
Peripheral gangrene
Musculoskeletal system
Arthritis, arthralgia
Gastrointestinal tract
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system
Urethritis/meatitis
Other findings
Erythema, induration at Bacille Calmette-Gue´ rin (BCG) inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
Laboratory findings in acute Kawasaki disease
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1§
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

* Patients with fever at least 5 days and ≥4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities detected by 2-D echocardiography or angiography.

† In presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many Kawasaki disease patients may establish diagnosis before day 4.

§ Some infants present with thrombocytopenia and disseminated intravascular coagulation.

Table 2. The differential diagnoses of Kawasaki disease

· Streptococcal infection (including scarlet fever, toxic shock-like syndrome)
· Staphylococcal infection (such as toxic shock syndrome or scalded skin syndrome)
· Measles, rubella, roseola infantum, Epstein Barr virus, influenza A and B, Adenovirus
· Mycoplasma pneumoniae
· Stevens-Johnson syndrome
· Systemic idiopathic juvenile arthritis
· Juvenile rheumatoid arthritis
· Rocky Mountain spotted fever
· Leptospirosis
· Mercury hypersensitivity reaction (acrodynia)

Changes in the extremities are distinctive. Erythema of the palms and soles or firm, sometimes painful induration of the hands or feet, or both erythema and induration often occur in the acute phase of the disease (Photo 1). Desquamation of the fingers and toes usually begins in the periungual region within 2 to 3 weeks after the onset of fever, and may extend to include the palms and soles (Photo 2). Approximately 1 to 2 months after the onset of fever, deep transverse grooves across the nails (Beau's lines) may appear.

An erythematous rash usually appears within 5 days of the onset of fever. The rash may take various forms; the most common is a nonspecific, diffuse maculopapular eruption (Photo 3).

Occasionally seen are an urticarial exanthem, a scarlatiniformrash, an erythroderma, an erythema-multiforme–like rash, or, rarely, a fine micropustular eruption. Bullous and vesicular eruptions have not been described. The rash is usually extensive, with involvement of the trunk and extremities and accentuation in the perineal region, where early desquamation may occur.

Bilateral conjunctival injection usually begins shortly after the onset of fever. It typically involves the bulbar conjunctivae (sparing the limbus, an avascular zone around the iris) much more often than the palpebral or tarsal conjunctivae; is not associated with an exudate, conjunctival edema or corneal ulceration; and is usually painless (Photo 4).

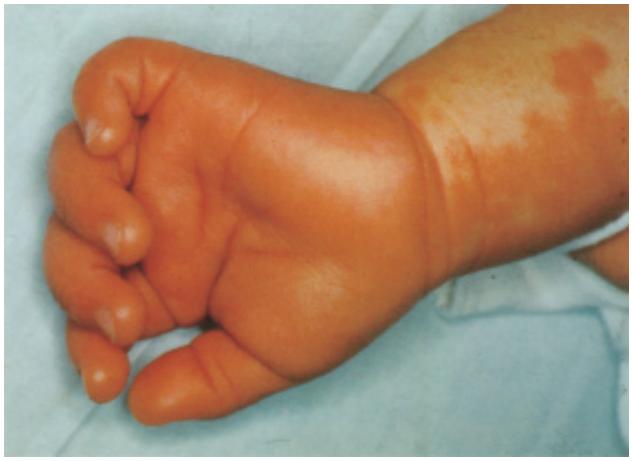

Photo 1. Reddening of hands

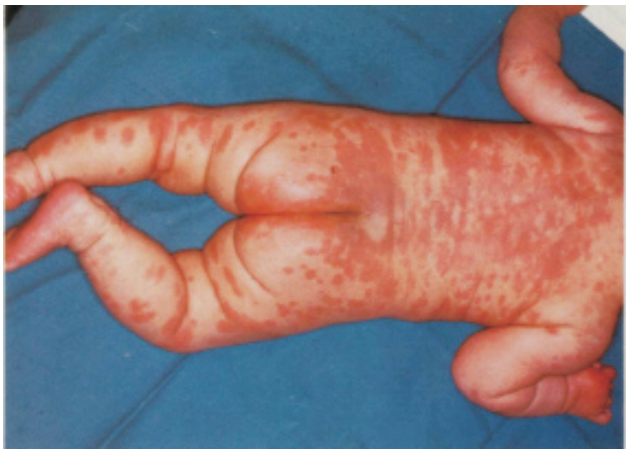

Photo 3. Exanthema

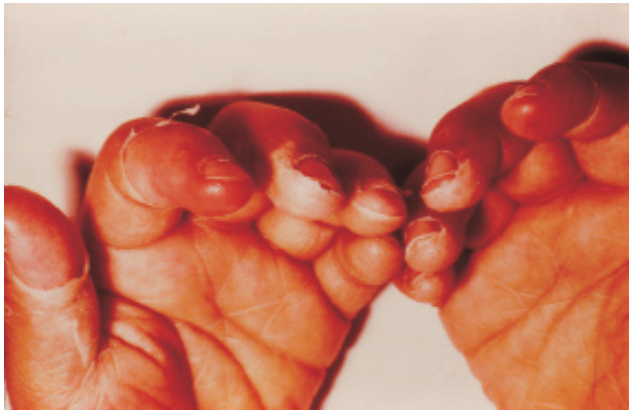

Photo 2. Membranous desquamation

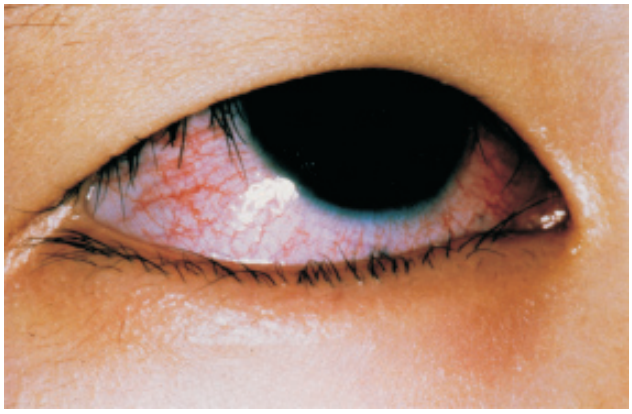

Photo 4. Conjunctival congestion

Changes of the lips and oral cavity include (1) erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips; (2) a "strawberry tongue" that is indistinguishable from that associated with streptococcal scarlet fever, with erythema and prominent fungiform papillae; and (3) diffuse erythema of the oropharyngeal mucosae. Oral ulcerations and pharyngeal exudates are not seen (Photo 5).

Cervical lymphadenopathy is the least common of the principal clinical features (Photo 6). It is usually unilateral and confined to the anterior cervical triangle, and its classic criteria include 1 or more lymph node(s) that is >1.5 cm in diameter. Imaging studies frequently demonstrate multiple enlarged nodes without suppuration. The lymph nodes often are firm and nonfluctuant, are not associated with marked erythema of the overlying skin, and are nontender or only slightly tender.[4,14]

Early diagnosis and treatment of KD is important; however, infants are unlikely to present with the classic signs and to meet the criteria of fever and at least 4 of the 5 other characteristic features. Patients found to have a C-reactive protein level >3.0 mg/dL and/or an erythrocyte sedimentation rate >40 mm/hr are advised to undergo supplemental laboratory testing and an echocardiogram. Patients meeting 3 or more of the supplementary laboratory criteria (albumin >3.0 g/dL, anemia for age, elevated alanine aminotransferase, platelets after 7 days ≥450,000/mm^3, white blood cell count >15,000/mm^3, and urine >10 white blood cells/high-power field) or with a positive echocardiogram should be treated with intravenous immunoglobulin (IVIG) for KD.[4,34]

Laboratory Findings

Different laboratory indices have been proposed by researchers not only as potential tools for the correct and timely diagnosis, but also as contributors in the disease pathology and its complications. Trivial markers of inflammation such as serum procalcitonin,[36] interleukin-[18,37] white blood cell count, and C-reactive protein (CRP)38 are all found to be elevated, not offering though much help in the determination of the severity and the differential diagnosis of the disease.

Leukocytosis is typical during the acute stage of KD, with a predominance of immature and mature granulocytes. Approximately 50% of patients have white blood cell counts ≥15 000/mm^3. Leukopenia is rare. Anemia may develop, usually with normal red blood cell indexes, particularly with more prolonged duration of active inflammation. Severe hemolytic anemia requiring transfusions is rare and may be related to IVIG infusion.[39-42] Elevation of acute phase reactants, such as erythrocyte sedimentation rate (ESR) and CRP, is nearly universal in KD, usually returning to normal by 6 to 10 weeks after onset of the illness. Furthermore, elevation of ESR (but not of CRP) can be caused by IVIG therapy per se; therefore, ESR should not be used as the sole determinant of the degree of inflammatory activity in IVIG–treated patients.

Differential diagnosis

Because the principal clinical findings that fulfill the diagnostic criteria are not specific, other diseases with similar clinical features should be excluded (Table 2). One of the difficulties of securing the diagnosis is that the clinical features of KD may appear sequentially rather than at the same time, and the feature most commonly identified is desquamation, which occurs late in the disease when cardiac complications may have occurred. Many of the differential diagnoses can be ruled out clinically; few have a fever that persists for longer than five days.[43,44]

The rash, oral and peripheral changes of scarlet fever are similar to KD, but the lymphadenopathy is more extensive and conjunctivitis is not seen. The rash in scarlet fever normally begins on day 2–3 of the illness, starting in the groins or axillae and rapidly spreading to the trunk, arms and legs. Seven to 10 days later desquamation occurs. The high fever ssociated with scarlet fever lasts 5–6 days. Scarlet fever responds readily to penicillin treatment or erythromycin for those allergic to penicillin.

Toxic shock and toxic shock-like syndromes are both associated with an ill child who may have erythema of the hands and feet, a diffuse non-specific rash over the face, trunk and limbs that desquamates, mucositis with oral involvement and non-exudative conjunctivitis. The patient

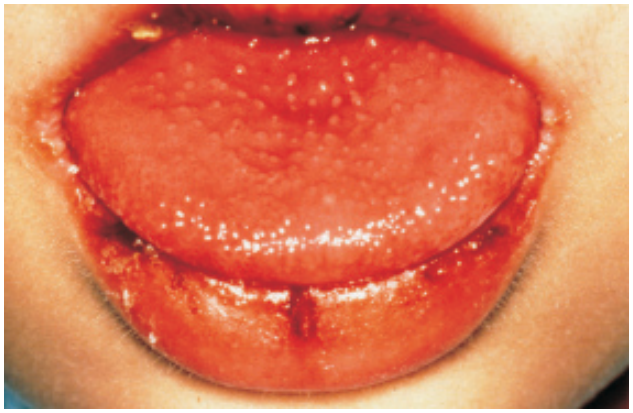

Photo 5. Reddening of lips and strawberry tongue

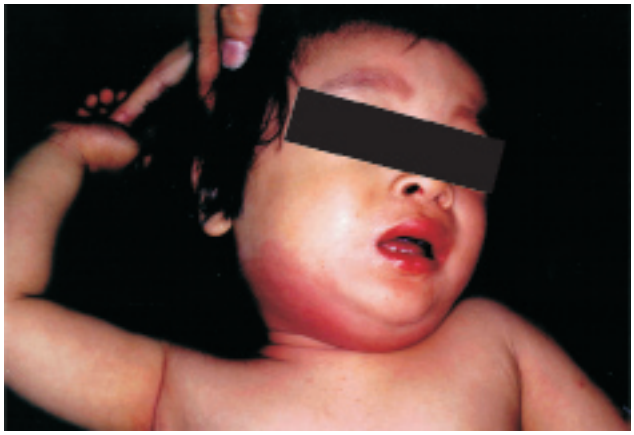

Photo 6. Cervical lymphadenopathy

needs urgent treatment with antibiotics and supportive therapy. The initial presentation of KD is not with shock.

Scalded skin syndrome is included as a differential diagnosis because there is a macular erythema that starts on the face and becomes more widespread; however, the epidemolytic toxin of Staphylococcus aureus (phage type II but occasionally I or III) causes bullae by separating intraepidermal layers, with the upper layers falling off. There is no mucosal involvement.

Measles mimics KD because there are many common features, namely the rash, non-exudative conjunctivitis, high temperature and generalised lymphadenopathy. In over half the cases of KD there is a solitary enlarged cervical lymph gland. The temperature in measles may exceed 40°C but tends to fall after day 5 of the illness. Koplik spots are not seen in KD and the morbilliform rash of measles begins from the ears and hairline, and starts to fade by day 4; after day 7 brownish staining may be seen due to capillary haemorrhage. Desquamation in severely affected cases of measles can occur but is not seen in the hands and feet. Rubella characteristically involves the cervical, suboccipital and post-auricular glands, which may appear up to a week before the onset of the rash. The rash comprises fine pink macules that coalesce on the face and trunk, spreading to the extremities, lasting for up to five days. The temperature in children is rarely above 37.4°C.

Roseola infantum has a sudden onset of fever up to 40°C, which lasts for 3 to 5 days. As defervesence occurs, a generalized macular or maculopapular rash appears on the trunk and neck which lasts for 1–2 days; it may also spread to the legs and arms. Cervical lymphadenopathy is seen, the suboccipital, posterior auricular and posterior cervical nodes being enlarged. The short duration of fever and absence of mucosal involvement excludes KD.

Epstein Barr virus causes infectious mononucleosis that predominantly affects older children, although an anginose form affecting the tonsils is seen in preschool children, which is associated with fever and sore throat with cervical lymphadenopathy, and the clinical picture is that of acute streptococcal tonsillitis. There is not commonly a rash in this form of Epstein Barr virus infection.

Infectious mononucleosis starts with anorexia, malaise and low grade fever that lasts for 1 to 3 weeks. There is often notable enlargement of cervical lymph nodes and splenomegaly is common. Rashes are seen in 10–15% of patients, the most common being a widespread maculopapular rash. Laboratory testing readily differentiates this condition from KD.

Influenza A in young children causes fever above 39°C, upper respiratory tract symptoms, and fleeting morbilliform rashes. The duration of the fever is 3 to 5 days at the most.

Adenovirus infection occurs mostly in children younger than 5 years and can have a number of presentations including pharyngoconjunctival fever with pharyngitis, headache, myalgia and unilateral or bilateral follilcular conjunctivitis, with exudation.

Mycoplasma pneumoniae, which may have a role in Stevens-Johnson syndrome, causes upper and lower respiratory tract disease, and is associated with a polymorphous rash and fever. There may also be generalised lymphadenopathy but rarely is there conjunctivitis, erythema of palms and feet or oral involvement.

Stevens-Johnson syndrome is characterised by erythema multiforme and causes erosive lesions at mucosal sites such as the conjunctivae and the oral cavity. The rash usually fades within 10 days, but there is a risk of superadded infection, which may cause widespread lymphadenopathy.

Systemic juvenile idiopathic arthritis may present with swinging fevers, systemic upset, and arthritis. The arthritis may not be present at the onset of the symptoms and varies from monoarticular to more commonly polyarticular involvement. Temperatures may exceed 40°C and last for at least two weeks. There must be one or more of the following extraarticular features: generalised lymphadenopathy (painless rather than painful in KD), rash (classically described as a macular pink fleeting rash), hepatomegaly (not a characteristic feature of KD) or serositis.[46]

Cardiovascular complications

Acute cardiac sequelae of KD

Cardiac sequelae include coronary aneurysms (Photo 7) and myocardial infarction, both comprising major causes of the morbidity and mortality related to KD.[47] Other cardiovascular complications include coronary artery stenosis, myocarditis, pericarditis with effusion, and mitral valvulitis.[7]

The incidence of cardiac sequelae in KD is falling. In a Japanese study of 69,382 patients with KD, 10,596 encountered cardiac sequelae and 15.3% of these occurred more than one month after the acute illness in more than 10 years ago, but it is 3.8% in recent days.[48] Risk factors for developing cardiac sequelae included male sex, age <1 year old, or >5 years old, CRP >100 mg/L, white blood count >30 x109/L 52, or low serum albumin.[49] In addition, those who received their medication late, after 6 days of illness, were more likely to develop complications.[50] Coronary dimensions are associated with the natural history of the aneurysms. Prognosis is reported to be the best when the aneurysms are fusiform and smaller than 8mm, and worst when the aneurysms are giant (>8mm).7 Study results conducted in Japan by linking the data for initial and second episodes of KD has shown that the risk of cardiac sequelae attributable to recurrent KD is high both in those with and in those without the sequelae at the initial episode.[51,52]

Coronary artery aneurysms

The above events result in coronary artery ectasia, mild dilatation up to 5mm across (small aneurysms), moderate dilation (up to 8 mm across) or giant aneurysms (>8mm).

Healing and fibrosis of the affected coronary arteries is seen later, leading to stenosis formation particularly in the post-aneurysmal segment of the artery, with the associated risk of coronary thrombosis, myocardial infarction, and sudden death.[53]

Treatment

Aspirin has been used in the treatment of KD for many years. High dose aspirin is initially used for its anti-inflammatory effect, but following the acute phase, the dose of aspirin is reduced to 5mg/kg/day, where it acts as an inhibitor of platelet function. This is continued for 6 weeks if no coronary artery abnormalities are present or longer whilst the coronary arteries remain abnormal. Aspirin does not appear to lower the frequency of the development of coronary abnormalities.[54] During the acute phase of illness, aspirin is administered at 80 to 100 mg/kg per day in 4 doses with IVIG.

Randomized, prospective clinical trials in the US in the 1980s established that IVIG was an effective and safe treatment, which reduced the rate of coronary artery lesions.54 IVIG treatment ideally should be instituted within the first 10 days of the illness,[55] but there may be some benefit in giving IVIG even after 10 days if there is evidence of ongoing inflammation.[56] The standard therapy in the US, United Kingdom, Europe, Australia, and Asia is a single dose of 2 g/kg IVIG infused over 10–12 h.[57] Side effects of IVIG depend on the infused product and range from fever, chills, and hypotension7 to increased blood viscosity and therefore risk of thromboembolism.[58]

A proportion of patients will fail to become afebrile despite treatment with IVIG and aspirin. For those where this has not been effective, most clinicians would attempt a repeat dose of IVIG at 2g/kg in order to achieve resolution of the inflammatory process.[59-61] Potential nonresponse to IVIG treatment should be considered among recurrent KD patients diagnosed and treated before the fifth day of illness, particularly when they are boys and when they have low platelet count, elevated alanine aminotransferase, and CRP.[62]

The role of steroids in KD

Corticosteroids are used additionally to the conventionaltherapy and have been found to shorten the duration of fever, accelerate the improvement of laboratory markers, and lower the levels of proinflammatory cytokines.[63] Treatment with plasma exchange comprises an important independent predictor of better coronary outcome.[64]

CONCLUSIONS

KD, a systemic vasculitis of infants and children, is one of the leading causes of acquired heart disease worldwide. Its cause is still obscure, involving various infectious agents, bacterial antigens, and allelic variations, all as possible causative or predisposing agents. Physical examination, laboratory markers of inflammation, and a case definition created for epidemiological surveys in Japan are the main tools currently available for the diagnosis of KD.

Treatment with aspirin and IVIG has improved the overall outcome; however, KD remains a major cause of acquired heart disease in children and may become a substantial problem for adults who had KD during their childhood.

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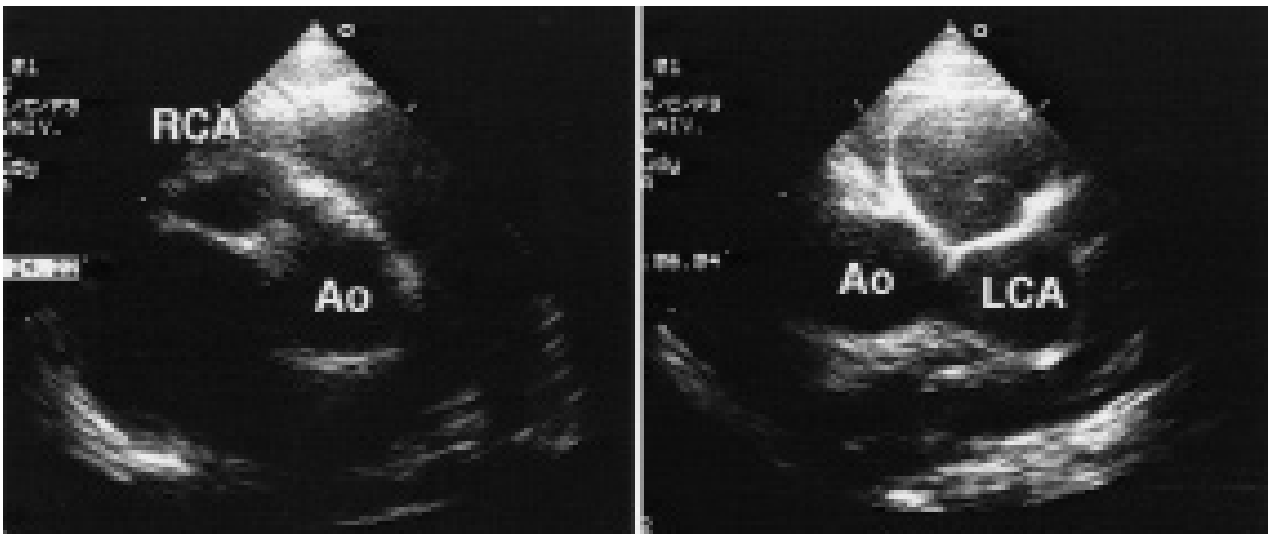

Photo 7. Echocardiograms of coronary anuerysms (Ao: aorta, RCA: right coronary artery, LCA: left coronary artery)

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A critical evaluation of the guideline of diagnosis and treatment for common diseases and disorders using Appraisal of Guidelines Research and Evaluation criteria

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ABSTRACT

Coronary heart disease is the largest cause of death in both developed and developing countries. Clinical practice guidelines have been elaborated to summarize evidence related to the management of coronary heart diseases and to facilitate an uptake of evidence-based knowledge by clinicians. The purpose of this study was to assess the quality of the guidelines using the internationally accepted criteria. The current existing guideline was independently evaluated by four appraisers using 23 items of the Appraisal of Guidelines Research and Evaluation Instrument. The current existing guideline was developed in 2005 and has 16 chapters, including a guideline for diagnosis and treatment of CVD (cardiovascular diseases) and rheumatism as the first chapter. Definition, causes, classification, clinical symptoms, risk factors, medical examination, clinical and biochemical laboratory tests, differential diagnosis, diagnostic and treatment procedures, and condition and time of treatment for ischaemic heart diseases and myocardial infarction were written in the II and IV subchapters respectively. There was not a large difference between appraisers' scores. As a result of the appraisal of the "Guideline for Diagnosis and Treatment of Common Diseases and Disorders," the standardized domain score ranged from 43.75% to 52.8%. In conclusion, it is possible to continue the implementation of the current existing guideline after making necessary changes and improvements according to the internationally accepted Appraisal of Guidelines Research and Evaluation criteria.

Key words

Guideline, appraisal, quality of care, coronary heart diseases, evidence-based medicine

INTRODUCTION

Coronary heart disease (CHD) is the largest cause of death, and is fifth largest in terms of burden in both developed and developing countries. By 2020, the low and middle-income countries will also have coronary heart disease as the most frequent cause of death and the greatest disease burden.[1,2]

Clinical practice guidelines have been elaborated to summarize evidence related to the management of CHD and to facilitate an uptake of evidence-based knowledge by clinicians. Clinical guidelines are defined by the Institute of Medicine as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances".[3] They are tools used by healthcare professionals to assist in clinical decision-making and to improve healthcare for patients. [4,5,6]

Over the past decade there has been a surge of interest in the use of clinical practice guidelines fueled by the discovery of large, unexplained variation in physicians' practices,[7,8] documentation of significant rates of inappropriate care,[9] and an interest in managing health care costs.[10] It is believed that practice guidelines can improve the quality, appropriateness, and cost-effectiveness of health care,[3] and can also serve as valuable educational tools.[11]

This emphasis is in part related to the relatively recent work of the Appraisal of Guidelines Research and Evaluation (AGREE) collaboration, an international collaboration of researchers and policy makers working together to improve the quality and effectiveness of clinical practice guidelines by establishing a shared framework for their development, reporting, and assessment.[12]

The purpose of this study was to assess the quality of the guidelines using the AGREE criteria.

MATERIALS AND METHODS

The current existing guideline "Guideline for Diagnosis and Treatment of Common Diseases and Disorders" and additional documents related to its development were study tools for the appraisal. The Appraisal of Guidelines Research and Evaluation (AGREE) Instrument was used as a tool for evaluation of the " Guideline for Diagnosis and Treatment of Common Diseases and Disorders in Mongolia". The AGREE Instrument, first published in 2001 assesses the quality of clinical guidelines according to the following 23 criteria, grouped into 6 domains such as (1) scope and (2) purpose, (3) methodology, (4) clarity

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and presentation, (5) applicability and (6) editorial independence.

The current existing guideline was independently evaluated by four appraisers using AGREE items. The appraisers were representative of policy-makers, members of the developing team of the current existing guideline, cardiologists following this guideline in clinical practice, and members of a research team.

Each item is scored on a 4-point Likert scale with answers such as 4-strongly agree, 3-agree, 2-disagree, and 1-strongly disagree. The scale measured the extent to which a criterion has been fulfilled.

Domain scores were calculated by summing up all the scores of individual items in a domain and by standardizing the total as a percentage of the maximum possible score for that domain. The overall judgment was scored with a 4-point categorical scale (not recommended, recommended with alterations, strongly recommended, or unsure).

RESULTS

The current existing guideline was developed in 2005 and is being used in all levels of health care organizations according to order #109 of the Minister of Health which was approved on 06th May, 2005.

This guideline has 16 chapters, including a guideline for diagnosis and treatment of CVD (cardiovascular disease) and rheumatism as the first chapter. The first chapter consists of 7 subchapters. Definition, causes, classification, clinical symptoms, specificity, risk factors, medical examination, clinical and biochemical laboratory tests, differential diagnosis, diagnostic and treatment procedures by care level and condition, and time of treatment for ischaemic heart diseases and myocardial infarction were written in the II and IV subchapters respectively.

1. Scope and purpose

This deals with the potential health impact of a guideline on society and populations of patients. The overall objectives of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem. The current existing guideline was not developed for only a single disease and disorder, Rather it is more complex and general. The overall objective and specific objectives were not formulated in the first chapter which is related to CVD including coronary heart diseases.

A detailed description of clinical questions covered by the guideline should be provided, particularly for key recommendations. For this guideline, eight clinical questions regarding main complaints, clinical symptoms, differential diagnosis and results of prescribed drugs were asked, and three key recommendations were given in accordance with above clinical questions in the second subchapter. These questions and recommendations are not proper and it is difficult to identify the most important key question and recommendation.

There should be a clear description of the target population to be covered by a guideline. A clear description of the target population including age range, gender, and comorbidity is not provided by the current guideline. But clinical symptoms of target groups with myocardial infarction and ischaemic heart diseases were written well and clear. Standardized domain scores of scope, purpose, description of clinical questions, key recommendations and target groups was 44.4% (Table1).

2. Stakeholder involvement

Items of this domain refer to the professionals who were involved in the stages of the development process, the consideration of patients' opinion and experiences, the definition of target users, and pilot pre-testing. The results of an assessment according to items of this domain are presented in Table 2. Members of the steering group, the research team and individuals should be involved in selecting, reviewing/rating the evidence and formulating final recommendations. Information about the composition, discipline and the relevant expertise of the guideline development group should be provided. All relevant stakeholders, including members of the steering boards, representatives of professional associations, coalitions, the research team, and specialists who work in hospitals have participated in the development of this guideline. Information about patients' experiences and expectations of health care should inform the development of clinical guidelines. There are various methods for ensuring patients' perspectives such as the involvement of patient representatives, information obtaining from patient interviews, and literature reviews

Table 1. Scope and purpose

Appraisers	Item 1	Item 2	Item 3	Total score
Appraiser #1	1	4	3	6
Appraiser #2	1	4	3	6
Appraiser #3	1	3	2	5
Appraiser #4	1	3	2	5
Total score	4	14	10	28
Standardized domain score				44.4%

of patient experiences. The appraisers did not find any evidence or documents related to involvement of patient representatives or the consideration of patient perspectives. There could be a lack of activities to consider patients' opinion, experiences, and perspectives for development of the current existing guideline.

The target users should be clearly defined in the guideline, so they can immediately determine if the guideline is relevant. For instance, the target users for a guideline on lower back pain may include general practitioners, neurologists, orthopaedic surgeons, rheumatologists and physiotherapists. In the current guideline, the target users were not defined clearly. Thus, it is difficult to determine for physicians if the guideline is relevant. However, all diagnostic and treatment procedures were written at a medical care level. Therefore, all target users can identify appropriate level care in the guideline. It means that all physicians who work in hospitals of secondary and tertiary care levels can use it.

A guideline should have been pre-tested for further validation among its intended end-users prior to the publication. This process should be documented. Pre-testing is very important for further validation and reliability of guidelines. There was not any evidence, documentation, or study findings of pre-testing which was done prior to publication to check its validity and reliability. The standardized domain score was 43.7% based on the assessment of all relevant stakeholders, patient representatives, the definition of the target users and the pre-testing procedure according to four items of the second domain of the AGREE.

3. Rigour of development

This domain was assessed according to seven items and the results were depicted in table 3. Details of the strategy used to search for evidence should be provided including search terms used, sources consulted, and dates of the literature covered. Sources may include electronic databases, databases of systematic reviews, hand searched journals, review of conference proceedings and other guidelines such as US National Guideline Clearinghouse, the German Guidelines Clearinghouse. Totally 38 references including 6 CPGs, 8 textbooks, 9 handouts and manuals, 10 scientific articles, 1 project report, and 4 electronic databases were used in development of the first chapter of the "Guideline for Diagnosis and Treatment of Common Diseases and Disorders". A few internationally accepted information sources were used for the development of the guideline because the authors and developers were not provided by the specific methodology.

Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described, and the reasons for including and excluding evidence should be clearly stated. For example, the guideline authors may decide to only include evidence from

Table 2. Stakeholder involvement

Appraisers	Items				Total score
	# 4	# 5	# 6	# 7	
Appraiser #1	3	2	2	1	8
Appraiser #2	4	2	3	2	11
Appraiser #3	3	2	3	2	10
Appraiser #4	3	2	2	1	8
Total score	13	8	10	6	37
Standardized domain score					43.75%

Table 3. Rigour of development

Appraisers	Items							Total score
	8	9	10	11	12	13	14	
Appraiser #1	3	3	3	3	1	4	2	19
Appraiser #2	3	3	2	3	1	3	2	17
Appraiser #3	2	2	3	3	1	4	2	17
Appraiser #4	1	2	2	3	1	3	2	14
Total score	9	10	10	12	4	14	8	67
Standardized domain score								46.4%

randomized clinical trials and to exclude articles not written in English. The authors of the current existing guideline have tried to use an evidence of the same level but some recommendations based on A-level evidence from recent randomized clinical trials were not recommended properly. From the appraisers' point of view this can be a consequence of not using the specific methodology including inclusion and exclusion criteria.

There should be a description of the methods used to formulate the recommendations and how final decisions were arrived at. Methods include, for example, a voting system and formal consensus techniques. Areas of disagreement and methods of resolving them should be specified. A description of the methods used to formulate the recommendations and final decisions of the current existing guideline was not written in the guideline. But the most needed recommendations of diagnostic and treatment procedures were written as a statement using the same writing type without any subtitle.

The guideline should consider health benefits, side effects, and risks of the recommendations. For example, a guideline on the management of breast cancer may include a discussion on various final outcomes. These may include: survival, quality of life, adverse effects, symptom management or a discussion comparing one treatment option to another. There should be evidence that these issues have been addressed. Survival, quality of life, and a discussion comparing one diagnostic and treatment option to another were written relatively less in the subchapters of either ischaemic heart diseases or myocardial infarction. Risk factors, health benefits, symptom management and complications of ischaemic heart disease and myocardial infarction were written based on study findings, citations from the textbooks and handouts more detailed in both subchapters. These were not described with evidence of randomized clinical trials according to international standards.

There should be an explicit link between the recommendations and the evidence on which they are based. Each recommendation should be linked with a list of references used. All references for developing recommendations were written at the end of the chapter, but it is not clear how to link recommendations and a list of references.

A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the development group and should have included experts in the clinical area, methodology and patient representatives. A description of the methodology used to conduct the external review should be presented, which may have included a list of the reviewers and their affiliation. The appraisers agreed that the current existing guideline was reviewed externally by the team which composed of 16 reviewers including a decision-maker, a policy developer, a member of the professional committee, advisors, and specialists prior to the publication. Representatives of physicians who work in hospitals and patients were not included in this team.

Guidelines need to reflect current research. There should be a clear statement about the procedure for updating the guideline. For example, a timescale has been given, or a standing panel receives regularly updated literature searches and makes changes as required. Therefore the appraisers assessed if there was a statement about the procedure for updating the current "Guideline for Diagnosis and Treatment of Common Diseases and Disorders". The current existing guideline did not provide any information about the editing date, responsible agency for updating, and duration of validity. However the order #109 of the Minister of Health was included in the guideline. This order has a special statement about informing further evaluation, and the difficulty of revising and developing the guideline. Thus the appraisers thought that there should be a statement that the guideline should be revised at least by updating the date, methods and clearly describing responsible agency. As a result of the appraisal the standardized score of this domain with the seven criteria was 46.4%.

4. Clarity and presentation

A recommendation of guidelines should provide a concrete and precise description on appropriate management of a particular situation and a patient group, as permitted by the body of evidence. For instance, a drug's name and type,

Table 4. Clarity and presentation

Appraisers	Items				Total score
	15	16	17	18	
Appraiser #1	4	4	2	1	11
Appraiser #2	3	3	2	1	9
Appraiser #3	3	4	1	1	9
Appraiser #4	3	3	1	1	8
Total score	13	14	6	4	37
Standardized domain score					43.75%

the dosage, and the duration should be described precisely. Indeed, all diagnostic and treatment procedures are more detailed and concrete because clinical practical guidelines are developed separately according to ICD. Namely, there is the guideline for management of acute coronary syndrome, the guideline for management of acute myocardial infarction etc. In Mongolia, there is a complex and general guideline for diagnosis and treatment of common diseases among a population. It was developed as a complex framework, and the authors tried to include many diseases and disorders in the guideline. Therefore, recommendations of diagnostic and treatment procedures were written more generally. The appraisers noted that the authors have tried to write a duration and dosage of some drugs to treat myocardial infarction and ischaemic heart diseases precisely in the II and IV subchapters. The result of the appraisal of this domain is shown in Table 4.

A guideline should consider different possible options for screening, prevention, diagnosis, or treatment of the condition it covers. These possible options should be clearly presented in the guideline. In our case, several possible options of diagnostic procedures and treatment were written comprehensively, and screening and prevention options were not considered well in the current existing guideline.

Users should be able to find the most relevant recommendations easily. These recommendations answer the main clinical questions that have been covered by the guideline. They can be identified in different ways such as a summary in a box, bold or underlined letters, flow charts, or algorithms. As a result of our appraisal, it is difficult to find the key recommendations from the guideline. These were not typed in bold, underlined, or summarized in a box. In addition the key clinical questions were not asked specifically. Therefore, it is not easy to identify the key recommendations which were based on these questions.

For a guideline to be effective, it needs to be disseminated and implemented with additional materials. These may include a summary document, a quick reference guide, educational tools, and patients' leaflets. The "Guideline for Diagnosis and Treatment of Common Diseases and Disorders" was disseminated without any additional materials mentioned above. Instead of these, official letters from the Ministry of Health and National Center of Health Development were disseminated with the guideline. All appraisers emphasized that these official letters can not be substituted for the reference guide, instruction and educational tools of the guideline. The standardized domain score of clarity and presentation of the current existing guideline was 43.75%.

5. Applicability

Applying the recommendations may require changes in the current organization of care within a service or a clinic, which may be a barrier to using them in a daily practice. Organizational changes that may be needed to apply the recommendations should be discussed. From the appraisers' point of view describing diagnostic and treatment procedures by health care level and defining referral conditions to the next level provided a great opportunity to increase the application of the current existing guideline. The score of the appraisers according to criteria of this domain are presented below (Table 5).

The recommendations may require additional resources in order to apply. For instance, there may be a need for more specialized staff, new equipment, and expensive drug treatment. These may have cost implications for a health care budget. There should be a discussion of the potential impact on resources in the guideline. The appraisers assessed that the recommendations in the guideline be developed based on human and financial resources of the health care system of Mongolia. As a result of this appraisal all recommendations concerning ischaemic heart disease and myocardial infarction in the guideline are appropriate to the level of care. There is no recommendation for expensive and practically unfeasible procedures in the guideline. The next updating stage of the guideline should focus on how to develop and include possible recommendations based on a country's economic situation and health sector's development. The standardized domain score for the guideline's applicability was 52.8%

Measuring the adherence to the guideline can enhance its use. This requires clearly defined review criteria that are derived from the key recommendations in the guideline. These should be presented. Examples of review criteria are: (1) HbA1c should be < 8.0%, (2) a level of diastolic blood pressure should be < 95 mmHg and etc. It is possible to measure the implementation of the guideline

Table 5. Applicability

Appraisers	Item 19	Item 20	Item 21	Total score
Appraiser #1	3	2	3	8
Appraiser #2	2	2	3	7
Appraiser #3	3	2	3	8
Appraiser #4	3	2	3	8
Total score	11	8	12	31
Standardized domain score				52.8%

based on a clinical diagnosis approved by the review criteria. Therefore these review criteria should be de described clearly and precisely in the guideline and identified easily. Diagnostic review criteria for ischaemic heart diseases and myocardial infarction including duration of chest pain, characteristics of pain, size of ST segment and pathologic Q wave, amount of cardiac biomarkers were written in the guideline. But they were not summarized in a box, typed in bold, underlined or presented as flow charts to be identified easily.

6. Editorial independence

Some guidelines are developed with external funding from charity organizations and pharmaceutical companies. Support may be given in the form of financial contribution for the guideline development, or for parts of it, e.g. printing of the guidelines. There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. In our case, "Guideline for diagnosis and treatment of common diseases and disorders" was developed and published with the technical and financial assistance of the WHO. There was not any support from other organizations and companies. In addition there was not any representative in the team of authors and developers from other companies, funds and organizations for profit. Thus there was no recommendation or statement which was influenced by the views or interests of above the organizations and companies.

There are circumstances when members of the development group may have conflicts of interest. For example, this would apply to a member of the development group whose research funded by a pharmaceutical company was covered by the guideline. There should be an explicit statement that all group members have declared whether they have any conflict of interest. As a result of the appraisal there was no recommendation that duplicated the meanings and associating authors' interests. The standardized domain score of the guideline was 50.0% based on the appraisal of editorial independence of the current guideline for diagnosis and treatment of major diseases and disorders among the population (Table 6).

The appraisers made their evaluation independently and there was not a large difference between the appraisers' scores (Table 7). As a result of the appraisal of the "Guideline for Diagnosis and Treatment of Common Diseases and Disorders" according to the AGREE criteria the standardized domain score ranged from 43.75% to 52.8%. All appraisers recommended the current guideline, but revisions and improvements are required to continue the implementation of this guideline.

DISCUSSION

The AGREE instrument tool is the first appraisal instrument which has been used for evaluation of the clinical guideline in Mongolia. Created through a rigorous and iterative process in collaboration with international experts in clinical guidelines, the instrument was applied to 100 guidelines by over 260 appraisers from 11 countries (13-15). These studies resulted in a rigorously developed set of criteria for appraising guidelines that can be helpful for clinical practice in two ways: (1) to help clinicians to differentiate between guidelines from different sources, and (2) to support the development of high quality guidelines for medical practice. In our case, the overall objective of the study to evaluate the current existing guideline was to support the development and revision of high quality guidelines for medical practice.

The results of the study, which was done within the framework of the AGREE collaboration, shows that the instrument is sensitive to differences in important aspects of clinical practice guidelines, and that it can be used consistently by a wide range of professionals from different cultural backgrounds [15]. We have similar results. As a result of our study, policy-makers, health professionals, and researchers were all able to appraise guidelines with the AGREE questions and a user guide. The appraisers found that the instrument easy to apply, and perceived it to be useful for judging the quality of guidelines.

The reliability of the domains is directly affected by the number of appraisers assessing one guideline. Thus, using four appraisers yield a more reliable assessment than using a single appraiser. [12,15,16] In this study, average ratings of four raters could provide the most reliable assessment.

As a result of our study, standardized domain scores

Table 6. Appraisal of editorial independence

Appraisers	Item 22	Item 23	Total score
Appraiser #1	4	1	5
Appraiser #2	4	1	5
Appraiser #3	4	1	5
Appraiser #4	4	1	5
Total score	16	4	20
Standardized domain score			50.0%

were as follow: domain 1-44.4% domain 2-43.75%, domain 3-46.4%, domain 4-43.75%, domain 5-52.8% and domain 6-50.0%. This result was quite similar comparison to the results from same studies. For instance, the results of the study was conducted within the framework of the AGREE collaboration were depicted that a standardized mean score of domain 1-6 were 69.3; 36.1; 40.7; 65.8; 36.9; and 30.3 respectively [15]. Another study conducted in the USA by JR. Cates and his team has shown that the American College of Occupational and Environmental Medicine Guidelines scored highest in the dimensions that evaluated reporting of the guideline's scope and purpose (79.63%) as well as clarity and presentation (86.81%).[17] The guideline scored much lower in the remaining areas that included stakeholder involvement (46.06%), rigor of development (26.59%), application (31.48%), and editorial independence (19.17%).

For the development of the Mongolian current existing guideline, the overall objectives were not specifically described, clinical key questions were not properly covered by the guideline and target users were not clearly described. The recommendations in the guideline were not specific enough, the different options for management of the condition were not clearly presented, and key recommendations were not easily identifiable. In addition, the guideline was not supported with tools for application. Therefore, standardized scores of these two domains were less in comparison with other study results.

Given the expansion of national guideline programs, governments and other agencies must ensure that the guidelines are of the highest quality before they endorse them or promote their use in practice. Professional organizations or groups should as well undertake a critical review of guidelines using available critical guideline appraisal tools.[18] Furthermore, as an international cooperation between countries grows there is a strong incentive for policy makers to develop a concerted approach to quality management initiatives, including clinical practice guidelines. The AGREE instrument can enhance this process.[19] This is already taking place as several agencies such as the National Institute for Clinical Excellence in the UK, the National Federation of Cancer Centres in France, the Agency for Quality in Medicine in Germany, and the Scottish Intercollegiate Guidelines Network are using AGREE in the context of their guidelines program. The WHO has adopted the AGREE instrument to assess its guidelines.[12,15] There is a real need to have governmental organizations, and other agencies or professional groups to be responsible for developing, implementing, revising, updating and assessing clinical practical guidelines across the country.

All the appraisers in our case thought the content of the guideline was substantially better than the documentation of the guideline construction process. The “Guideline for Diagnosis and Treatment of Common Diseases and Disorders” appeared to have consistent content, but the reporting of the guidelines construction process, particularly the rigor of recommendation development, is flawed, and the recommendations may not be valid because of problems in selecting potential evidence.

In an international practice, a key indicator is the perception of developers to address the issues necessary to produce a good quality guideline, and a decision of potential users to use the guideline. Rather than splitting guidelines into good or bad, the instrument provides a numerical description of a guideline in six domains. This allows potential users to relate a guideline to the whole population of guidelines and then to decide on the basis of their requirements. For example, a hospital interested in introducing a guideline for the management of acute myocardial infarction may want to look at guideline (1) because it scores high on clarity and presentation, but also to review guideline (2) owing to its rigour of development. This approach could provide a quality dimension to the database of guidelines that are now emerging in Canada,[20] America,[21] and Germany. [22]

As for stakeholder involvement, it appears that a change in the attitude of guideline developers is needed. Guideline developing teams tended not to include all relevant stakeholders and patients. It is, however, suggested that involving stakeholders in a guideline elaboration tends to improve applicability of the recommendations and to facilitate appropriation among end users.[23] Although there is evidence describing ways to facilitate AGREE collaboration, (24,25) guideline developers are perhaps unaware of literature relating patients’ view or are uncomfortable in sharing power and responsibilities, especially with patients. In an AGREE evaluation of several guidelines, very similar results were obtained.[23,26]

The AGREE evaluation of the guideline for the management of knee osteoarthritis demonstrated that the guidelines effectively addressed only a minority of domains. Although scope and purpose, rigour of development and clarity and presentation were the most often effectively addressed domains, the majority of guidelines failed to appropriately address these domains.[27] In our case, these domains were not well addressed while developing the guideline. Guideline developers should focus on the AGREE criteria constituting these domains in the elaboration of future guidelines.

It appears that the AGREE criteria are more and more taken into account when elaborating guidelines. The two most recent guidelines [28,29] had the highest quality and were the only ones mentioning the use of the AGREE instrument in the elaboration. Even these guidelines, however, failed to effectively address the majority of domains. Producing a high-quality guideline effectively addressing all AGREE domains appears to remain a challenge.

In conclusion, the developing team of the “Guideline for Diagnosis and Treatment of Common Diseases and Disorders” focused on stakeholders’ involvement, the first

two items of the domain on clarity and presentation, applicability and editorial independence more effectively during the development of the guideline. But the most important parts including scope and purpose, rigour of development, and the last two items of the domain, clarity and presentation, were not considered carefully. However, several items of the domains of the AGREE were not emphasized during the development of the guideline. It is possible to continue the implementation of the guideline after making necessary changes and improvements according to internationally accepted AGREE domains criteria.

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Identification of gaps in child and adolescent mental health system in Mongolia

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ABSTRACT

The goal of the research was to promote the development of Mongolia's child and adolescent mental health policy, services and training with providing systematic information on relevant country resources. This research has been conducted through three subsequent stages using the CAMH-ATLAS questionnaire developed by the WHO for collecting information on child and adolescent mental health resources. The results show somewhat small rates of mental health services in the society, especially in health care, while continuing to represent substantial gaps in policy, financing, service, human resources, and data collection, even undeveloped or fragmental child and adolescent mental health system in Mongolia. The findings point to an invaluable role for the policy development, suggesting that an implementing institution must be established and function as the mental health service in collaboration with other health, education, and juvenile justice sectors for children and adolescents.

Keywords
Child, adolescent, protection, psychiatry, mental health

INTRODUCTION

Child and adolescent mental health service in Mongolia that started from 1961 is now in urgent need of reform and appropriate country or regional commitment, as mental health service is concerned with improvements in care to adults with serious mental illness. These should be demonstrated through policy, legislation, and governance.[1] According to some related studies conducted in Mongolia, 12% of 1765 people who had committed suicide and 25% of 3134 people who had attempted suicide were children and adolescents aged 10-19.[2] Twenty five percent of all children involved in the study reported that they were oppressed from other peers and 47% of the children with disabilities reported that they feel stigma and discrimination from others.[3,4]

The emphasis of this paper is systematic information on relevant country resources, including both governmental and non-governmental activities among children. The goal of the study was to stimulate the development of necessary child and adolescent mental health policy, services and training with providing systematic information. The survey had the following objectives; gathering information on child and adolescent mental health system, identifying the gaps on this system, and formulating an advocacy for the development of child and adolescent mental health policy and program

MATERIALS AND METHODS

The current study used Child and Adolescent Mental Health ATLAS-questionnaire developed by the World Health Organization (WHO) for collecting information on child and adolescent mental health resource. The details of the study design and instruments used have been described elsewhere.[5]

Briefly, in the preparing stage key organizations thought to be most informed about the available resource in the country were selected from the use of services in four sectors: health (National center of mental health (NCMH), psychiatric units in general hospitals, Infants and maternal research center, Clinical sanatorium for infants, Detoxification center, Primary health care units), education (Public schools, Special education school), child welfare (Social services, Children's homes), and juvenile justice (Detention center, Prison for female criminals) including governmental agencies as well as non-governmental organizations (NGOs). The available information on existing resources in the literature, relevant to the child and adolescent mental health, were collected and analyzed for preparing a glossary of terms, cross-checking the new information and supplementary questions as well as clarifications to the key organizations. The structured questionnaire is a 10 domains questionnaire consisting of questions about

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the demographics, policy and legislation, financing, mental health services, human resources, non-governmental organization, World health organization, care for special population, and medications and other treatment modalities.

In the data collecting stage representative samples were obtained from informants of the 61 selected key organizations and interviewed in person or by telephone after filling the questionnaires.[5] For data entering and analysis we used MS-Excel and SPSS-11.

RESULTS AND DISCUSSION

1. Demographics

In 2006, Mongolia had 2.59 million (2594700) population. In regard to age groups, the proportion of the population aged less than 15 years was 28.6% and for the age group of 0-18 years was 41.5% (1076817).[6] Three percent of 841 users per 100000 populations visited the mental health outpatient facilities were children under 15 years.[7] In addition, 2.8% of 21714 registered patients to the outpatient clinic of the NCMH were children suffering from severe mental disorders and 26.5% of them were received medical care in the inpatient section of NCMH.[8]

2. Policy and Legislation

Mongolia has no identifiable child and mental health policy and legislation. However, Mongolia has developed over 300 provisions that include aspects on children and adolescents at national policy documents, programs, and legislation on protecting the rights of children as well as adopted international written documents such as United Nation (UN) Convention on the Rights of the Child (1990), World Declaration to "Provide conditions for healthy growth, defense and development"(1990), New Horizons in Health (1995), Cairo Declaration on Population and Development (1999), and UN Convention on the Rights of the People with Disabilities (1971).[9]

Some provisions and statements of the Constitution of Mongolia (1992), Law on Protection of Child's Rights (1996), Law of Health Insurance (1997, 2003), Mongolian Social Security Law for People with Disabilities (1998), Law of Social Welfare and Care (1999), Law of Labor (1999), Law of Mental Health (2000), and Law of Education (2002) are closely relevant to the child and adolescent mental health and serve to protect the rights, support social care, promote education, provide medical services, and cover the health insurance for children and adolescents. These themes are reflected in several national programs including: Improving the Development and Protection of the Child until 2010 (2002), Mental Health (2002), Inclusive Education for Children with Disabilities (2003), Improving the Quality of Life of the People with Disabilities (1998), Health education for the Population (1998), Health Education for School pupil and Adolescent Health (1997-2005), Development of Sanatorium (2003), Fighting against iodine deficiency (2002), Preventing from accidents and injures (2002), Improving physical strength of the citizens (2002), Reproductive Health (2001), National Program of Action for the Development of Children (1996-2000), and School pupil and Adolescent Health (1997-2005).

3. Financing

The main resource for child and adolescent mental health services is a tax-based Government funding. The Government funding totally covers health care expenditures of children under 18 years, the expenditures for specialized education program, and allocates social allowance to the family with children with disabilities as benefit (monthly 40500 Mongolian tugrugs-MNT). In 2006, the government spent a total of 74.5 billion MNT for children as social aid and service through Ministry of Labor and Social Welfare that represents 2.34% of the total GDP (3172.4 billion MNT)

In 2006, over 80 million MNT were spent for division of child mental health and cabinet of child psychiatry of the NCMH, which represents 6.7% of the total expenditure (1.19 billion MNT) of the NCMH or 0.07% of the Total Health Expenditures (103.1 billion MNT).[10] Although, the government spent 342 million MNT for Special education service, 0.36% of the expenditure were for Secondary education service (93.72 billion MNT) which creates 48% of the total expenditures of education, culture, and science (195.2 billion MNT).[6] (Figure 1)

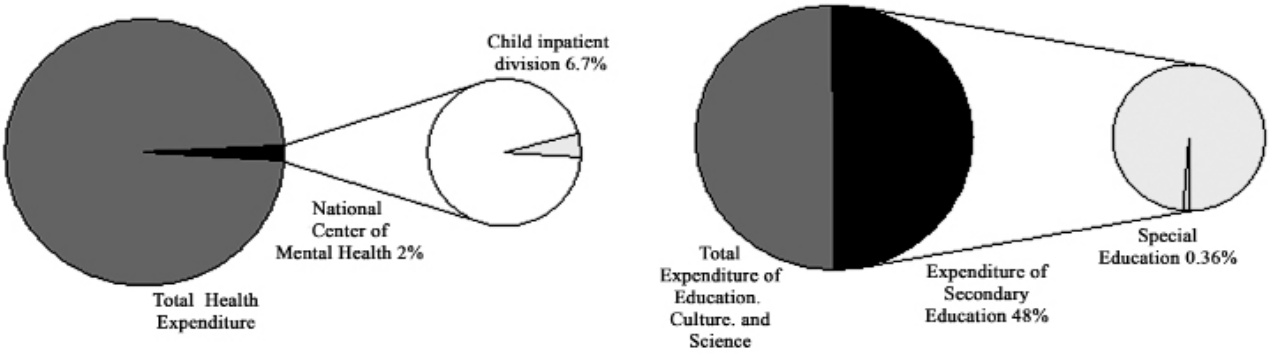

Figure 1. Expenditures of child and adolescent mental health and educational services (2006)

The other sources of funds are international or national NGOs such as UN agencies, Save the Children United Kingdom, World Vision Mongolia, ADRA, and ICM of the Vatican representatives, though their expenditure reports are not available for reference.

4. Services

Mongolia does not have any separate or affiliated specialized institution or governmental entity with clearly identifiable overall responsibility to the child and adolescent mental health system yet. Child and adolescent mental health services are supported to varying degrees by ministries of education, health, and social welfare without coordinating legislation, guidelines, and standards. However, there are some existing services in regards of WHO-recommended optimal model of services for children with mental disorders.[11]

It is a fact that self-care management for prevention or treatment of mental disorder is significantly poor due to misconception, stigmatization, and discriminization against children with mental illnesses among the population.[3, 4] The information on child development, developmental crisis, school related problems, and mental disorders given by different media to the population are not up-to-date or scientifically based, even though there are actually 27 newspapers, 8 journals for children as well as 1 public and 11 private televisions preparing weekly 77 hour entertainment and education programs for children in Mongolia.[6]

The services at the public schools (742), children's homes (7), children's foster care centers (47) and prisons (2) do not focus on promotion of mental health and primary prevention of mental disorders and trainings in child mental health for the workers are insufficient.[9,12] Since 1998, under the School based health education program the training curricula and manuals for public school teachers have been developed in different health related subjects including 11 hours for mental health.[13]

There are only 7 state sanctioned organizations, children's homes. Clinic inpatient institution for infants, established in 1966, has 118 health professionals including pediatricians, nurses, a social worker, a speech therapist and a psychologist which providing complementary health and rehabilitation service for 90 children under 3 years old.[14] Forty seven international NGOs promoting, educating, and supporting children in foster care centers do not report their activities to the governmental agencies and the ethics of social and health care of them for children in Mongolia has been unknown.[15]

Law on Protection of Child's Rights of 1996 mandates the means to facilitate the implementation of rights through the establishment of a National Children's Council under supervision of Prime Minister and its implementing agency National Centre for Children in every bigger administrative unit throughout Mongolia.[10] National Centre for Children under supervision of Deputy Minister provides a framework for focused action on protecting the rights and resource mobilization for the comprehensive promotion of healthy development of children and adolescents through providing a pleasant environment and needed services by coordinating other services of governmental and non-governmental organizations.[16]

The impact of the National Committee of Human Rights, founded in 2001 under the Parliament, was dramatic in its effects assuring the verification of human rights to all people living in Mongolia through implementing the national program, promoting and monitoring all activities that protecting human rights.[17] The focus of the work of the Political Lobbying Group for promoting the development and protection of children is on policy making including awareness increasing, lobbying, and public campaigns for children.[9] These child protecting organizations pay very scarce attention to the cross-sectoral prevention and promotion initiatives on child mental health.

Community based mental health care for children and adolescent is not available apart from few small day treatment centers which are offered by international NGOs (i.e.World Vision Mongolia). There are powerful multidisciplinary teams consisting special education teachers, teachers, pediatricians, psychologists, social workers, and rehabilitators with additional training in child mental health in the Special Education Services.[18] Special education school is an educational organization that offers primary, basic, upper secondary and vocational education (9 years of education) through flexible and easy curricula and methods designed for children with disabilities. These children have lost their physical or mental capability caused by congenital and non congenital etiology, congenital abnormality, diseases, injuries, and has no ability to work under normal conditions because of visual, hearing, or speech impairment, physically disability, mental retardation, or mentally abnormal behavior. The special education in Mongolia refers to the type of education designed for children with mental, speech, visual, and hearing needs.[19] The first special education school for children with disabilities was found in 1967 in Ulaanbaatar and the number of those schools increased to 11 in 1990s but decreased again to 6 in 2006 due to the National Program on Inclusive Education for Children with Disabilities.[20]

In 2006, 38569 children with disabilities studied in the public schools including those of special education schools.[21] More than 68% of 1850 children studied in the special education schools had mild mental retardation and the reasons of the disabilities were hereditary, prenatal disorders and birth complications or unspecified.[22] Special educational services lack rehabilitative, curative, professional orientation training and social supporting service for children with mental illnesses. Not only at the special schools but also in the entire community as public schools, children's homes and prisons early detection and treatment of children and adolescents with mental illnesses, espe-

cially specific developmental disorders of scholastic skills, hyperkinetic disorders, and conduct disorders lacking due to absence of integrated health care service by trained child psychiatrists.

The health care system in Mongolia is characterized by three levels of services. Primary health care, whether physician based or non physician based, consists of 34 inter-county clinics, 288 county clinics, and 224 family practices in municipalities including 1336 physicians and 4266 beds.[23] Seventy percent of the primary health care clinics and practices provide mental health service to the population.[7] There is no available data about the number of visits of children with mental health problems, education about mental health issues, and screening at the health care centers.

In 2006, secondary health care services providing mental health care through psychiatric cabinet for the population included 9 general hospitals in Ulaanbaatar and 18 general hospitals in provincial municipalities, aimag hospital, and 4 regional diagnostic and therapeutic centers.[24], 25 In most of the cases, children with mental health problems visit pediatricians and then psychiatrists in secondary health care. There are no special beds for children. Three general hospitals in regional municipalities have no beds for psychiatric patients.[25] After the foundation of the Adolescent health cabinets in 1998, the most provinces now have Adolescent health cabinets, but majority of them were established in the bases of gynecological cabinets. Gynecologists pay attention to physical health of children, but not the mental health.[13]

As the first institute provided child mental health care in Mongolia since 1963, the Maternal and Child Research Center (former Child hospital) does not have outpatient and inpatient child mental health care, except a speech therapy unit. The reason of the reform is the foundation of child psychiatry cabinet at the Mental hospital and Medical school of Mongolian state university in 1965.[26] According to the revisions of the Ministry of Health, the Child and Maternal Research Center is responsible for the child health care except of the mental health care and in case of psychiatric illnesses diagnosed at the Center the needed service will be provided by consultation psychiatrists from the National Center of Mental Health or the patient will be located to the child inpatient division of the NCBH (Sharkhad hospital).

Since 1965, there are no identifiable high specialized separate or affiliated institute, group home, foster care placement at any level or within any sector of health care in Mongolia. However, a unique long-stay facility for children with serious mental health problems in whole country is the child inpatient division with total 26 beds at the National center of mental health. The division (8th division) refers specialized diagnostic and treatment, consultation, and rehabilitation service for children. There are 1 psychiatrist, 1 chief nurse, 3 nurses, and 6 nurse assistants working at the unit, but none of them including the psychiatrist has received a specialized training in child and adolescent psychiatry.[8] Eleven out of the total 26 beds in the section are allocated to the children with severe or profound mental disorders and retardation who are transferred from the Labor therapy and care home, Maanit hospital, after its abolition in 2003. In fact, only 15 beds were available for all children with mental disorders in Mongolia. Rehabilitation of children is limited and has been developing with the helps of ICM, ADRA, and World Vision Mongolia. An average length of stay is 58,[9] days twice that of adults.[8] Child outpatient cabinet of the NCMH refers investigation, diagnostic service, and day treatment and has 1 non-specialized psychiatrist and 1 nurse.[8]

5. Human resources

During 1964-1990, totally 3 psychiatrists had received specialized training in child and adolescent psychiatry in the former Russia.[26] Now there are 0.5 psychiatrists trained in psychiatry for 2 years, 4.7 psychiatrists trained in psychiatry for 1 year or 6 months, and total 5.2 psychiatrists and 2.2 pediatricians per 100000 populations of Mongolia.[7]

An in-country child and adolescent psychiatry training program does not exist. Since 1965 the Department of Mental Health of Health Sciences University of Mongolia has been developing the child and adolescent psychiatry training module programs with 14 hours for medical students in graduate study and 60 hours for resident students in post graduate study.[27] The training program for residency course in pediatrics does not include any of mental health issues.[28]

While approximately 40 teachers in the special education schools graduated defectologist-teacher (special education teacher) in Hungary, Poland and former Russia, the

Table 1 . Human resources in mental health in different countries (rate per 100000, 2006)

Human resource	Mongolia	Russia	Japan
Psychaitrists	5.2	13.3	9.4
Child psychiatrsts	0	0.84	0.23
Psychiatric nurses	7.6	50	59
Psychologists	0.2	1.9	7
Social workers	0	1.2	15.7

Resource: WHO (2007). Countries" mental health profiles

other professionals did not trained in child psychiatry at all. In the special schools there are at least 10 speech therapists who work with children with specific developmental disorders of speech and language. The most of the workers in the organizations, supported by international and inland NGOs promoting mental health wellbeing of children are volunteers or non-health workers and have not received trainings in child psychiatry.[29] (Table 1)

6. Non-Governmental Organizations (NGOs)

Except the UN agencies, international and national NGOs including World Vision Mongolia, ICM of the Vatican representatives, Save the Children UK, and ADRA are collaborating actively to promote advocacy, policy development, human right protection, training, and rehabilitation for children with some components of child and adolescent mental health.[9] They have initialized and sponsored some child mental health programs, for instance, "Community-based health care for children with mental disorders" project by World Vision Mongolia, "Hot ail"-Education and shelter for street children project and "School social workers" program through Save the Children, "Smoking free youth" project by ADRA-Mongolia, and Health Education 1998-2000 Open Society Institute, SOROS.

7. World Health Organization (WHO)

While WHO has provided enormous assistance in the development of mental health services directly or through its regional office in Mongolia, it has not supported any program or project on child and adolescent mental health.

8. Data Collection and Quality Assurance

Data on epidemiological and service issues including child mental health issues from the whole country related to mental health are collected at the NCMH and approved at the National center of health development.[10] Annual Health Indicators, developed by National center of health development, does not present mental child and adolescent disorders separately. There are no national standards of care expected from professionals working in child and adolescent mental health but maintained through in-service training.[10] The current reporting system of the health care does not reflect WHO-classification category by age groups.

There are no scientific newsletters and journals specialized in child psychiatry, even a list of publications in Mongolia. Since 1961 a total of 50 publications were issued on child psychiatry issues including 4 textbooks and booklets, 8 doctoral and master's dissertations, 28 scientific articles, 3 developed training programs, and 5 public articles.

In 2006, 7% of children under 19 years among 21714 patients were registered in the Outpatient service of the NCMH due to mental health problem. But only 2.7% of 5955 patients who received inpatient health care at the NCMH were children and adolescents. There are 450 beds at the NCMH including 26 beds for children. The average length of stay in the child inpatient division is 58.9, twice longer than adult divisions. [28] (Table 2)

Descriptive analysis of Outpatient clinic data showed that 658 children under 15 years were registered (6.3 per 10000 children) and 140 were diagnosed for the first time during 2004-2006. A mental retardation was the most common disorder among children with psychiatric illnesses. Regarding the morbidity of the children mental retardation, organic mental disorders, and neurosis were the leading disorders. (Table 3)

9. Care for Special Population

Children with mental health-related problems of Kazakh and Tuva people, or minority ethnic groups in Mongolia, have not adequate access to necessary health and educational service due to language barrier and geographical location. There were 51002 orphans, 1128 homeless or runaway children in 2006.[12] Forty six children died out of 159 natural disaster-affected children in 2006, and this number was increased by 3 times in 3 years.[6]

10. Medications and Other Treatment Modalities

There is no National Essential Drug List of medications for children and adolescents in Mongolia and pharmaceutical drugs for children and adolescents are not identifiable separated in the psychoactive drug list. [30] Among psychoactive drugs, tricycle antidepressants, antipsychotics, and anxiolytics are widely used for children in the primary

Table 2. Some statistical indicators of child inpatient and outpatient facilities (2006)

Population	Registered in the Outpatient controlling		Placed in the Child Inpatient Division		Total beds in the country		National Center of Mental Health			
	Number	Percentage	Number	Percentage	Number	Percentage	Beds	Percentage	Average length of stay	Bed occupancy
Total	21714	100	5955	100	648	100	450	100	28.3	13.2
Children	1512	6.9	162	2.7	26	4	26	5.7	58.9	6.3

Resource: Annual reports of National Center of Mental Health

health care system but resource is limited and prescriptions are required. Prescriptions of the psychoactive drugs are controlled by reviews of the Narcotics National Control Board and must be written by trained health professionals only. Due to limited resources these medications are sold by market price for the population. Only registered users of outpatient service of the NCMH can receive sometimes free medications or with discounting price of 10%.[7]

Actually child and adolescent routine mental health care uses mainly medicinal therapy and limited psychosocial rehabilitation, psychotherapy, speech therapy, balneology, undeveloped children's home services, and relative stable educational supports.

The results show significant gaps in mental health service in Mongolia, especially in policy, financing, service, human resource, and data collection that represent a current undeveloped child and adolescent mental health system. An implementing institution should be established for children and adolescents in collaboration with health, education, and juvenile justice sectors.

Based on the survey findings advocacies for increasing awareness of consequences of the poor mental health among children address the following key activities in further development of child and adolescent mental health system:

- Formulate the child and adolescence mental health policy, plan, and program
- Establish a core implementing instance with providing funding and technical supports and promote the human resource
- Promote and strengthen the integration and collaboration of the related organization at any levels and sectors, for instance to increase professional mental health resources within schools, to enhance mental health service in the child protection organizations, children's homes, foster care placements, and juvenile justice system
- Broaden and stimulate the care shift from psychiatric hospital to community-based services in promoting of consumer groups, families, and NGOs to participate in those of activities
- Initialize further academic studies on epidemiology of mental disorders, particularly the mental retardation, conduct, developmental disorders, and suicide and also needs assessment surveys with medical universities, so that define prior activities
- Take educational activities towards prevention, screening, diagnosis, and treatment among health professionals working all health care levels, especially training of general practitioners in child and adolescent mental health
- Develop quality improving standards on child mental health care and follow at all health care levels for balancing the needs of different groups and assuring equity
- Conduct activities with the media to raising attention to mental health, improving knowledge, understanding of mental disorders in the general population and educating the persons working in the mass media, aimed at changing misconceptions, stigmatization, and discrimination.

ACKNOWLEDGMENT

This project was supported by HPSR grant from the World Health Organization. The fieldwork for this study was supervised by Prof. Byambasuren S and consulted by Dr. Nalini Sharma. Dr. Altanzul N helped with collecting information. The authors acknowledge with gratitude the help of Assoc.Prof. Ganbat B. The authors also appreciate the cooperation of the entire community participated in this study.

Table 3. Prevalence and incidence rates of children under 15 years in the Outpatient controlling of the Child outpatient cabinet (per 10000 children, 2004-2006)

Mental disorders (ICD-10)	Prevalence				Incidence rates			
	2006	2005	2004	Average	2006	2005	2004	Average
Mental retardation F70-F79	3.7	3.6	5.4	4.2	0.9	0.7	0.8	0.8
Organic mental disorders F00-F09	1.2	1.3	1.3	1.3	0.2	0.3	0.3	0.3
Mental disorders with onset usually occurring in childhood and adolescence F90-F98	0.3	0.3	0.4	0.3	0.1			
Neurotic, stress related and somatoform disorders F40-F49	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2
Schizophrenia, schizotypical and delusional disorders F20-F29	0.1	0.1	0.1	0.1				
Disorders of psychological development F80-F89	0.1		0.1	0.1				
Mood disorders F30-F39			0.1					
Total /F 00- 99/	5.6	5.7	7.5	6.3	1.4	1.3	1.4	1.3

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Improvement of first aid during injuries

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ABSTRACT

Knowledge and skills necessarry to carry out the first aid for injury is important in order to save human life and health. The main objective of this study is to determine the forms of injury, its types, characteristics, frequency, and the current state of providing first aid during the occurrence. We also propose standards directed at improving the quality of first aid in accordance with the needs of the patients. The research involved a total of 920 people, who admitted to the Receipt Units of the Injury Rehabilitation Clinic and Center for Burning and Poisoning in Ulaanbaatar between 18 and 25 of April, 2005. The leading cause of injuries was lack of knowledge and skills of the individuals who were present at the accident site to deliver first aid, accounting for 49% of the injuries that did not received the post-injury first aid. Only 51 or 5.5% of all 920 study subjects attended first aid training. More than seven percent of injured people called the ambulance; 23.3% were delivered to the hospital whereas 69.1% admitted themselves to the hospital and received the hospital care.Traffic and domestic accidents, as well as violence are the main types of population injuries in Mongolia. The knowledge and skills of citizens, doctors, nurses and other medical professionals for providing first aid following accidents are insufficient. The proportion of people who received first aid at the accident site was very low and was dependent on the type of injury.

Key words: Injury, first aid, policy, training, kit, supplements

INTRODUCTION

First aid policy in the world was initially directed towards wounded soldiers during the war.[1-3] The scope and direction of first aid has been changing since the twentieth century.[4-6] Five million people annually (on average 16000 people a day) are losing their lives due to injury, whereas 600 million people are becoming invalids as a result of injury. It is estimated that the mortality due to injury will reach 8.4 million by 2020.[7]

In Mongolia, a total of 2603 persons (80% male and 20% female) died due to injury in 2004, accounting for 10.3% of the total population mortality. This is expected to increase, reaching 11.1% in 2005 and 11.3% in 2006.[8] The problems associated with providing first aid haven't been sufficiently addressed either at the level of professional medicine or at all levels of the educational curriculum. There are limited research projects that have been conducted on the frequency of injuries in Mongolia, their types, causes, complications, mortality, the provision of first aid and its quality.[9] The main objective of this study is to determine the types of injuries among the population and the conditions and situations of first aid being provided, as well as any additional measures to be taken. We also aimed to prepare standards directed at improving the quality of first aid to meet the needs of the patients.

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MATERIALS AND METHODS

The research involved all 920 patients who applied for or were delivered to the Receipt Units of the Injury Rehabilitation Clinic (IRC), Center for Burn and Poisoning in Ulaanbaatar between 18 and 25 April, 2005. The causes and types of injuries were determined using research cards that included information from the patients, their family members, and doctors of the emergency department. To determine the knowledge, experience and approach of those who were providing first aid among the citizens, medical and mid-level professionals, we used "face-to-face" interviews and testing. The information about first aid during occurrences of injuries, the current situation of the service, problems encountered, ways of solving them, and the training quality were collected through group discussions. The curriculum for first aid of secondary schools, the Mongolian Red Cross society, the National emergency management authority, the Medical University and college, and driver's schools have also been assessed using an assessment sheet through referencing the related legal acts and documents.

RESULTS

Among the 920 patients included in the survey, 88.7% were admitted to the Clinical Rehabilitation Hospital, while 16.5% who are aged 0-19 years were admitted to the Center for burns in Ulaanbaatar. Six hundred and three (65.5%) patients were male and 317 (34.5%) were female. When admitted to the hospital 831 (90.3%) patients were able to provide information on the questionnaire by them-

selves but the remaining patients were unable to be interviewed. More than 23.3% of all patients had used alcohol when admitted to the hospital. The types of injuries among all study subjects are shown in the Figure 1 and by age groups in Table 1, respectively.[10]

Thirty nine percent all study subjects and 51.0% of those aged 0 to 19 years had been injured due to domestic injuries, 29.9% of study subjects and 35.7% of people aged 20 to 54 years were injured due to violence, whereas 14.7% of the total patients and 23.5% of people of age above 55 years were injured due to traffic accidents. Analysis of the relationship between the causes of injuries and the age showed a statistically significant association ($p<0.05$). The status of provision of first aid immediately after the injury in regard to the types of injuries is shown in Table 2. One hundred and fifty (16.3%) subjects out of the total patients surveyed received first aid immediately after sustaining the injury. The provision of first aid on site depended on the type of injuries ($p<0.05$). It was provided more frequently during sporting (33.3%) and industrial (26.9%) injuries compared to traffic injuries (14.1%) and violence injuries (16.0%).

During first aid, only 6.0% of the 150 cases had sufficient kits, 70.7% had insufficient kits and 23.3% had no kit for providing the first aid. Fifty one out of 920 study subjects had attended training courses on providing first aid, which was different by age groups: 5.9%, 7.2% and 1.6% among people aged 55 and over, 20 to 54, and 10 to 19, respectively ($p<0.01$) (data not shown).[10]

DISCUSSION

Traffic accidents are the main cause of mortality among the population. The number of mortalities caused by injury exceeded the base index of the "National program for injury prevention", reaching 100 per 100000 population. This shows that special attention is needed for implementation of the program. However, the previous study results showed that 68.5% out of 280 people between the age of 16 to 45 in Ulaanbaatar City had no knowledge of or practice in providing first aid during occurrences of injuries.[11] This is in agreement with the results of our current survey.

In order to implement the health care policy of the Government, to prevent injuries, and to resolve problems, the Government of Mongolia has developed a "National Programme Control for Injury Prevention", that began in 2002. The results of the program show that the illness level caused by injuries has increased from 274.55 per 10000 people in 2002 to 365.56 in 2007; stationary patients due to injuries from 86.22 per 10000 people in 2002 to 105.9 in 2007; the mortality due to injuries from 76.6 per 100000 people in 2002 to 116.9 in 2007 respectively. On the other hand, an important criterion for the social health of the program has been excluded and neglected without consideration. The issue of how many people have been included in the training courses for teaching and re-teaching first aid to the citizens and medical professionals during the project implementation period annually, and how to calculate, control and appraise the results of the training courses, has not been reflected in the reports 2003/2007.[7]

Table 1. The proportion of injuries' types by age group

Types of Injuries	Age groups (%)			
	0-19 (n=255)	20-54 (n=614)	55 + (n=51)	Total
Domestic injury	51.0	34.4	41.2	39.3
Industrial injury	2.7	6.8	5.9	5.7
Traffic injury	12.5	14.8	23.5	14.7
Sport injury	7.1	2.0	0.0	3.3
Violence	17.3	35.7	23.5	29.9
Others	9.4	6.3	5.9	7.2
Total	100	100	100	100

Table 2. Status of first aid delivered on site immediately after the injury

Causes of the injury	Number of person	Received first aid after injury (%)	
		Yes	No
Domestic injury	362	17.1	82.9
Industrial injury	52	26.9	73.1
Road and Traffic injury	135	14.1	85.9
Sport injury	30	33.3	66.7
Aggressive violence	275	16.0	84.0
Others	66	1.5	98.5
Total	**920**	**16.3**	**83.7**

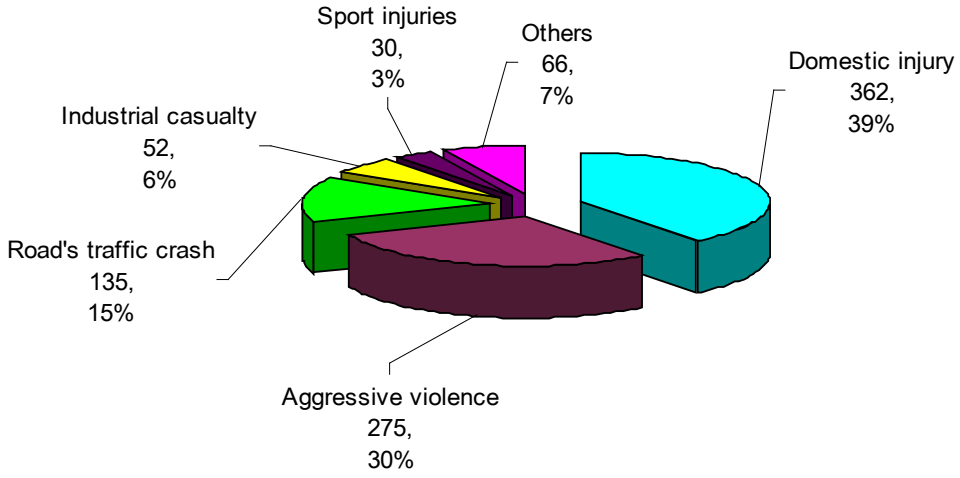

Figure 1. Main causes of injuries by number and percentage

Doctor Flabouris A, Bridgewater works for St. John Ambulance service in Australia. They did analyses of demand for first –aid care at a major public event. Mean patient presentation rate was 1.9+/-0.47 per 1.000 show attendees. This correlated best with the maximum daily temperature (r=0.715, p=0.02) and show day (r=0.615, p<0.05). There was poor correlation with daily attendance (r=-0.235, p=0.54). Mean presentation time was 15:13 hours. Of those whose gender was recorded, 58.4% were females, and 41.6% were males. The most frequent age group was 13 to 20 years. The nature and number of initial symptoms are listed. Basic first aid skills were used for 96.7% of symptoms; 2.4% of patients were referred to the hospital. It could be concluded from this that basic knowledge of the first aid during occurrences of injuries is sufficient. I It is important to study and implement training programs in first aid.[12,13]

Some studies previously conducted in Mongolia showed that 750 children have undergone injuries in the Capital City in 2001, of which 13 died due to these injuries. Studies of the causes of injury show that 4% children were playing on the road, 29% were running on the road, 15% were due to leaving small children unsupervised, 13% due to hindering of vehicles and 38% were due to wrong actions of the drivers. Our study shows that 60% were caused due to poor supervision of the parents and teachers of secondary schools as well as the actions of the children themselves. This is in agreement with our research.[14,15]

The cases of injury in injuries the population of Mongolia has been increasing the net increase of injuries and poisoning per 10000 population recorded at the outpatient wards between 1997 and 2006 has increased by 16.09 cases with an average growth rate of 5.7%. Injuries resulting from traffic, domestic accidents and violence are predominant among the population.

The knowledge, skills and approach of the general practitioners, nurses and mid-level professionals as well as citizens to provide the first aid during occurrences of injuries are insufficient and appropriate programs and training courses are needed for general population. The proportion of those who have received first aid on site immediately after the injury was very low, and it was also associated with the unavailability of the first aid kits.

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Influence of Numrugt Banzdoo (Saussurea involucrata Kar et Kir.Sch.Bip) plant polysaccharide on the immune complement system

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ABSTRACT

Saussurea involucrata is a traditional Mongolian medicine used in the treatment of purlulent lung infections, lung fever and wound fever. The objective of this investigation was to study the influence of the acidic and neutral pectin obtained from Numrugt Banzdoo (Saussurea involucrata Kar e t Kir. Sch. Bip) on the complement consumption assay. Four preparations of neutral and acidic polysaccharides extracted from Numrugt Banzdoo were studied at six different concentrations ranging from 15.6-500 mg/ml. We investigated the ability of these extracts to inhibit hemolysis of human blood by sensitized sheep red blood cells (SRBC) by standard methodology. We conclude that all 4 preparation made from Numrugt Banzdoo are more active than Plantago major II (acidity 50ºÑ ICH50<15, acidity 100ºÑ ICH50<15, neutral 50ºÑ ICH50<15, neutral 100ºÑ ICH50=23, Plantago major II ICH50=28). It is clear from the results in Table 2 that the ICH50 of 3 preparations (all but the neutral one) at 100ºÑ is twice as active as than of Plantago major II . The preparation from Numrugt Banzdoo has a relatively small molecular weight and high yield. We consider that it is possible to use and introduce it into practice as an immune adjuvant and to use it against different kinds of inflammation alone or in combination with other preparations.

Key words: Saussurea involucrata, reaction, pectin, Polysaccharides

INTRODUCTION

Forty nine species of Banzdoo grow in Mongolia. Numrugt Banzdoo grows on the mountain ranges of Mongolia, Khuvsgul, Khentii, Khangai, Mongolian Altai and Gobi-Altai where the damp soil of mountain plateaus is covered with grindstones and rocks.[1] The part of Numrugt Banzdoo that grows above the ground contains flavonoids (0.4%) and alkaloids (1.68-1.73%), carbohydrate, and ether oil.[2] In Mongolia traditional medicine Numrugt Banzdoo is used for treatment of purlulent infections, lung fever, wound fever and for weakening the contraction of smooth musle.[3] In previous studies, it was determined that Saussurea involucrata has anti-inflammatory properties, choleretic effect and dilatation of bronchi and atony of intestine muscle.[4] Polysaccharides extracted from some plants used in traditional medicine improve immune function. Glucans with a geterogen structure, which do not belong to the arabinan group, are present.[5] All neutral and acidic polysaccharide fractions of Saussurea involucrata had very high activity. Neutral fractions of both the 50ºC and 100ºC aqueous extracts of the parts of the plant above ground were rich in 1, 5 Ara (16.2% and 29.3% resp), 1, 3, 5 Ara (11% and 20.6% resp) and MW 15K, and were present in both fractions. Acidic fractions of both the 50oC and 100oC aq. extract had 1,4 linked GalA 30.6%, 35.7% respectively, and linkages characteristic of AGI.[6] Therefore, to study the influence of Numrugt Banzdoo pectin polysaccharides using a complement consumption assay will help in providing answers of theoretical and practical interest to medicine. The objective of the investigation was to study the influence of the acidic and neutral pectin of Numrugt Banzdoo (Saussurea involucrata Kar e t Kir. Sch.Bip) using the complement consumption assay.

MATHERIALS AND METHODS

Numrugt Banzdoo plant samples were prepared during the flowering phase in Chandmani soum, Gobi-Altai aimag in Mongolia in July and August. Chemical analysis has been done at the School of Pharmacy, Oslo University Norway and at the Institute of Chemistry and Chemical Technology, Mongolian Academy of Sciences.

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Complement consumption assay of pectin polysaccharides

1. Preparing human serum for investigation

Blood was taken from healthy volunteers who did not smoke or drink an alcohol. It was collected in vacuteiners and was centrifuged at 37°C at a speed of 1000 revolutions/min. for 10 minutes. Natural antibody against sheep blood red cell- (SRBC) was prepared in the following ways: 3 parts of washed sheep red blood cells (with 2 mm EDTA for the total mixture) was placed into 2 parts serum and left for 30 minutes at 0°C, after which it was centrifuged. Calcium chloride (5mm) was added to clear the serum and it was stored at 70°C. This was designated "the preparation containing human serum complete complement" (Michaelsen et al.1991).7 Packed sheep red blood cells were washed twice with 0.9% sodium chloride and then washed with physiological saline (calcium chloride. 0.2mm; magnesium chloride, 0,8mm; cow serum albumin, 2 mg|ml (bovine serum albumin, BSA), acid sodium, 0.02%) balanced with verinal buffer (VB) to pH-7.2. SRBCs were used as a 1% suspension in VBS/BSA. rabbit blood anti serum (Virion amboceptor 9020, Ruschilikon, Switzerland) prepared against sheep red cells at a dilution of 1:4000 was added and incubated at 37°c for 30 minutes. The sensitized cell suspension was washed three times and spun. It was used as a 1% suspension.

2. Phases of the complement consumption assay (Michaelsen et al.2000)

Samples of the polysaccharides were prepared at different dilutions in VBS/BSA. In our study we used 500., 250., 62.5., 31.25.,15.625., 7.812 mkg/ml. 50mkl from each dilution was placed in a micro plate with a circular bottom and 50mkl serum added. This was centrifuged at 37°C for 30minutes at a speed of 1000 revolutions/min. for 2 minutes. 100mkl from the top liquid was placed on a microplate with a flat bottom and light assimilation measured with an instrument called a MR700 Microplate^{R} Reader (Dynatech) at a wave length of 405nm. Water was used to produce 100% hemolysis.

The degree to which each dilution of carbohydrate inhibited red cell hemolysis was determined by the following formula and is described in the graphics (Michaelsen et al.2000) Each analysis was done twice and the results averaged.

Erythrocyte hemolysis obstruction,%=[(Acontrol -Asample)/ Acontrol]õ100%

Based on the results obtained the concentration which caused hemolysis of 50% ICH of sheep blood cells was determined by PRISM software and program (GraphPad Software, SanDiego, CA, USA)

RESULTS AND DISCUSSION

Influence of polysaccharides of the Numrugt Banzdoo plant on the complement system

Six different dilutions, ranging from 15.6 to 500mg\ml were made of the neutral and acidity polysaccharidesfrom Numrugt Banzdoo. The ability of these extracts to inhibit the hemolysis of snsitized SRBCs was determined. The average results are shown in Table1. The tortuous inhibitory curve was drawn, and SRBC hemolysis 50 inhibition (ICH_{50}) was shown. The ICH_{50} for action of the neutral and acidity polysaccharides of Numrugt Banzdoo is shown in Figure 1 and Table 2.

When the ICH_{50} of pectin polysaccharides is smaller, the influence of the preparation to complement formulation is larger.

We compared the action of these pectin polysaccharides to that of Plantago major L (PM II), which has been structurally and biologically well studied and is known to powerfully influence the complement system. We conclude that all 4 kinds of preparation made from Numrugt Banzdoo are more active than PMII. As seen in Table 2, the ICH_{50} of 3 kinds of preparation (all except the neutral fraction at 100íÑ) are two times more active than PM II.

The preparation from Numrugt Banzdoo is of relatively small molecule weight and high yield, so we consider

Table 1. Influence of preparations made from neutral and acidic polysaccharides of Saussurea involucrate on sheep sensitive blood cell hemolysis

Sample cons, mkg/ml	Inhibition of sheep red blood cell, %				
	PM II*	Neutral polysaccharide		Acidity polysaccharide	
		50íÑ-ä S.I**	100íÑ-ä S.I**	50íÑ-ä S.I**	100íÑ-ä S.I**
15.6	37	87	39	87	80
31.2	52	94	66	95	92
62.5	70	97	82	97	96
125.0	86	97	91	98	97
250.0	94	97	93	98	98
500.0	97	99	97	99	99

*Taken as a well studied comparative substance with high influence *Plantago major L* polysaccharid- PM II preparation
**Polysaccharide of examining plant *Saussurea involucrate*

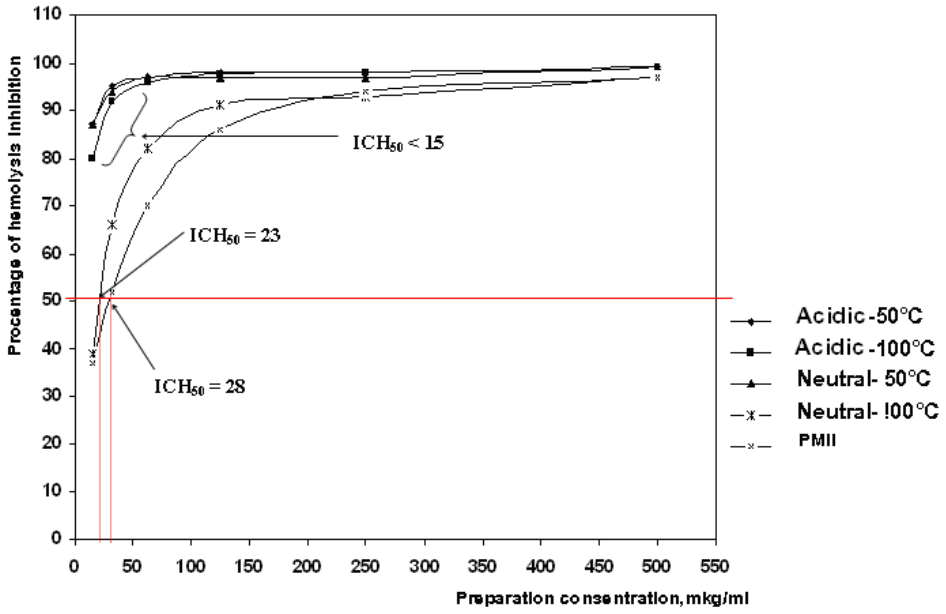

Figure1. Inhibition of sheep red blood cell hemolysis by preparations of the acidic and neutral polysaccharides of *Saussurea involucrate*

that it is possible to introduce it into practice as an immune adjuvant and use it alone as an anti-inflammatory agent. Further study using polysaccharides of Numrugt Banzdoo in combination with other preparations is needed.

Some researchers studied the interaction between a pectin type PMII isolated from the leaves of *Plantago* major and human complement in two different hemolytic complement-fixation tests and also detected complement-activation products by two ELISA (enzyme-linked immunosorbent assay) methods. The results showed that PMII is a potent complement activator with an activity of the same order of magnitude on a weight basis as that of aggregated human immunoglobulin (Ig) G. The researchers demonstrated that PMII is an activator both on the classical and the alternative pathway of activation.[8]

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Table 2. ICH_{50} values of the neutral and acidic polysaccharides of Saussurea involucrate on sheep sensitive red blood cell hemolysis

¹	Preparation	ICH_{50} Values
1	*Saussurea involucrata*, neutral polysaccharide 50ºÑ	15<
2	*Saussurea involucrata*, neutral polysaccharide100ºÑ	23
3	*Saussurea involucrata*, Acidity polysaccharide 50ºÑ	15<
4	*Saussurea involucrata*, Acidity polysaccharide100ºÑ	15<
5	*Plantago major* L, PMII	28

In vitro examination of salivary gland cells in sialolithiasis

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ABSTRACT

The chemical composition and structure of stones in the salivary glands and ducts among Mongolian patients have been studied in our previous studies. In the current study we described the genes of bacteria associated with sialolithiasis in order to determine of etiology of sialolithiasis. A total of 50 micro samples were prepared from salivary gland tissues taken during the surgery from patients with sialolithiasis to study the histological and cytological changes in the salivary gland using microscopy. In the sialolithiasis samples there were calcifications, inflammation of fat infiltrated gland tissue and decrease of acinis cells and atrophy. We cultured the submandibular and parotid salivary gland cells, extracted the RNA and used real-time PCR to quantity. The level of expression of alkaline phosphates, type I collagen osteocalcin, osteopontin in RNAs. The level of expression of alkaline phosphates, type I collagen osteocalcin, osteopontin were higher in the adenovirus infected cells than in control samples. Massive calcification, decrease of acinis cells number, fat infiltration and replacement of parynchematous tissue by the fibrous are common in sialolithiasis of submandibular salivary gland. Gene expressions of type 1 collagen, osteocalcin, osteopontin, alkaline phosphatase were relatively high in adenovirus infected HSY salivary gland cells.

Key words

Sialolithiasis, salivary gland, sialolith, pathological tissue, cell

INTRODUCTION

There are submandibular, lingual and parotid salivary glands in the human body. The etiology of sialolithiasis, its chemical composition and structure and the occurrence of histological and cytological changes have attracted the attention of researchers since the 1930 s. Studies of researchers Clementev and Afanasiev showed that sialolithiasis is found in 20.7- 78% of all salivary gland pathologies and 2.9- 7% of all oral diseases.[1,2] Massaferi and Kiyachko[3] reported a higher prevalence of sialolithiasis in children and young adults. Sialolithiasis constituted 1.2% of total morbidity in some countries,[4] and almost 90% of all cases occurred in submandibular gland.[5] In the studies of Seifert and colleagues 30% of sialolithiasis cases were accompanied by inflammation and 3% by tumors.[6] Salivary gland inflammation was detected in patients with sialolithiasis in a studies that used Magnetic resonance imaging (MRI) and Computed tomography (CT).[7] Adjiev [8] reported a tissue atrophy and increase of fibrous tissue in the affected salivary gland in sialolithiasis. The *in vitro* experimental study of Japanese researchers suggested that sialolithiasis is treated with dihydroxyvitamin D3l.[9]

According to our previous study, sialolithiasis composed 3.8% of total oral diseases. In Mongolia there were no previously conducted studies on sialolithiasis. Therefore in this study we investigated 50 Mongolian samples and determined histological and cytological changes by molecular biology methods *in vitro.*

MATERIALS AND METHODS

Salivary glands' biopsies were taken at the Maxillofacial surgery Department of the Central State Hospital at the Tokyo Medical and Dental University and Health Sciences University of Mongolia. A total of 50 micro samples were prepared which were investigated with 10 X40 loop on a microscope (Carl Zeiss, Oberkochen, Germany) for the determination of histological changes in salivary gland tissues. The cells of HSG (submandibular gland) and HSY (parotid gland) were cultured, infected/ treated/ with Bone Morfogenetic Protein -2 (BMP-2) adenovirus. Then we defined the alkaline phosphatase, type 1 collagen, osteocalcin, osteopontin gene expression level in the infected parotid gland cells and compared them with those in non-infected cells. For the determination of type 1 collagen, osteocalcin, osteopontin gene expression, the spe-

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cial primer was used in Real Time-PCR (RT-PCR) for the direct determination of alkaline phosphatase activity level. Type 1 collagen, osteocalicin, osteopontin proteins in the BMP adenovirus infected parotid cells were extracted and studied by Polyacrylamyde Gel Electrophoresis (PAGE) at the molecular biological laboratory of the Department of Oral Pathology, Tokyo Medical and Dental University.

RESULTS

By the investigation on the laser scanning microscope, there were massive calcifications (Figure.1), fat tissue infiltrate (Figure.2), decrease of alveolar cells (Figure.3), and fibrous atrophy of adenoid epithelium (Figure. 4) in the salivary gland tissue. Type 1 collagen, osteocalcin, osteopontin gene expression was determined as absent or low in non- infected HSG, HSY salivary gland cells. As shown in Figure 5, these gene expressions were relatively high in BMP-2 adenovirus infected / treated/ HSY salivary gland cells. By the Polyacrylamyde Gel Electrophoresis conducted on proteins extracted from BMP-2 adenovirus infected / treated/ HSY salivary gland cells, the proteins usually produced in bone tissue like type 1 collagen, osteocalcin and osteopontin (Figure. 6).

Comparison by the staining method of alkaline phosphatase activity levels in infected and non- infected HSY cells showed that the non- infected cells were negative for alkaline phosphatase activity level. On the other hand, the infected cells were positive or had high activity level of alkaline phosphatase (Figure.7).

DISCUSSION

Our research results showed that sialolithiasis is caused by parenchymatous tissue inflammation; this is similar with outcomes of Misa Sumi Masahiro (1999) that reported about presence inflammation in sialolithias detected by MRI or CT.[7] The massive calcifications were defined to occur in sialolithiasis in the current study that is in accordance with the studies of Lustmann J and colleagues (1990).[10,11] They showed the presence of calcium in salivary gland stones.[10-12] Studies of Koichi,[6] Nakamura[7] and Adjiev[8] reported the decrease of acinis cell number, fat tissue infiltration, parenchymatous tissue atrophy, increase of fibrous tissue in sialolithiasis, which are similar with our outcomes. We agree with the conclusions of researchers that showed the osteoponin, osteocalcin, alkaline phosphatasa gene expression influence to the occurrence of salivary gland calcification and scarring.[13-15]

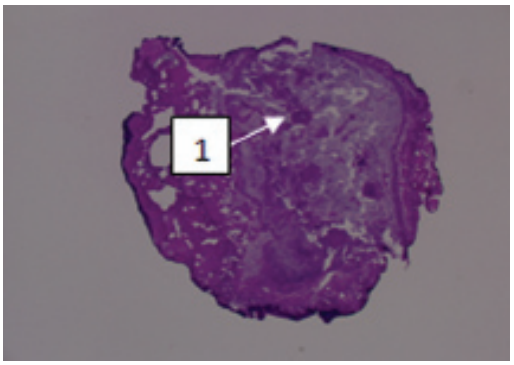

Figure1. Calcification in salivary gland using hematoxylin-eosine as a color substance (10x20).

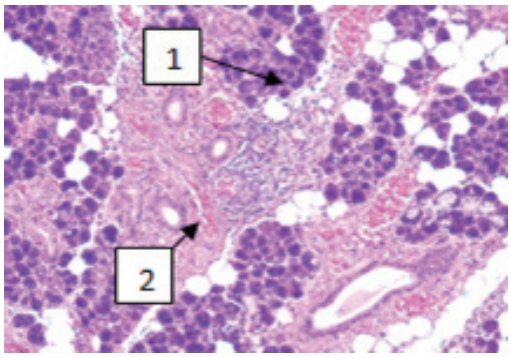

Figure 3. 1. Acinis cells of the salivary gland. 2. Size of the salivary gland and acinis cells number decrease. Hemotoxylin-eosin (10x20).

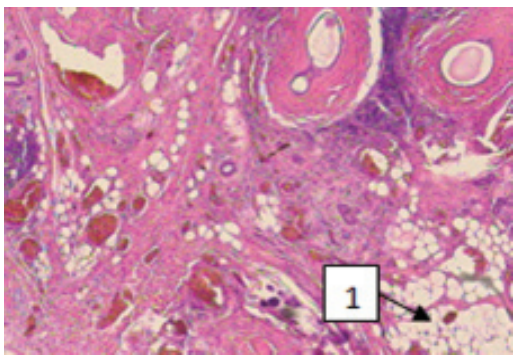

Figure 2. Fat tissue infiltration. 1-Fat cells with peripherally displaced nuclei Hemotoxylini-eosin (10x20).

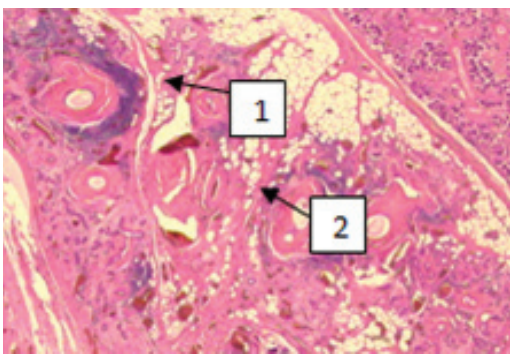

Figure 4. 1. Fibrous atrophic, gialin gland epithelium 2. Line like mononuclear cell infiltration ininterstitial gland. Hemotoxysin-eosin (10x20).

In conclusions, massive calcification, decrease of acinis cells number, fat infiltration and replacement of parynchematous tissue by the fibrous are common in sialolithiasis of submandibular salivary gland. Gene expressions of type 1 collagen, osteocalcin, osteopontin, alkaline phosphatase were relatively high in adenovirus infected / treated/ HSY salivary gland cells.

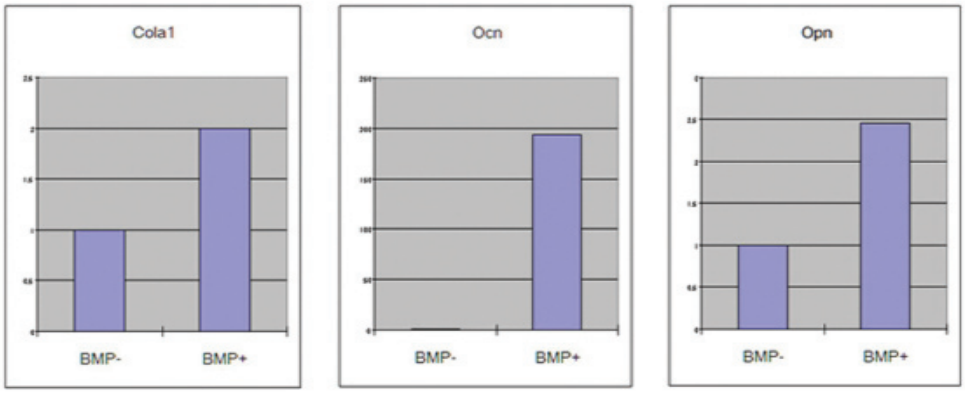

Figure 5. Level of expression of collagen 1, osteocalcin and ostiopontin in infected and non-infected HSY cells by BMP2 adenovirus.

Cola 1, Collagen 1; Ocn, osteocalcin; Opn, ostioponin
BMP -, Bone Morfogenetic Protein adenovirus not-infected
BMP +, Bone Morfogenetic Protein adenovirus infected

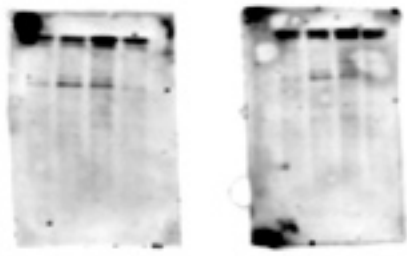

Figure 6. The extraction status of type 1 collagen, osteocalcin, osteopontin protein in BMP-2 adenovirus infected / treated/ HSY salivary gland cells by Polyacrylamyde Gel Electrophoresis

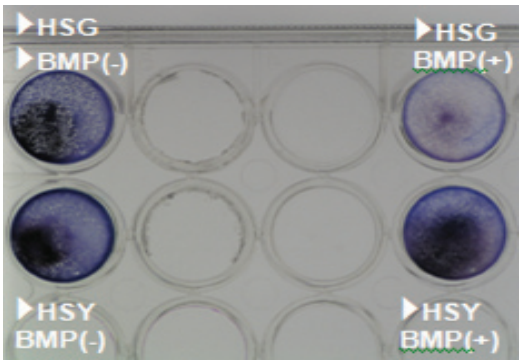

Figure 7. Determination alkaline phosphatase activity level in salivary gland cells.

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