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HIGH ALTITUDE DISEASE ON THE TIBETAN PLATEAU[1]

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ABSTRACT. In China, the Qinghai-Tibetan plateau is the highest and largest plateau in the world, in which lives both Tibetan natives and Chinese immigrants (Han). This paper deals with questions concerning high altitude disease (HAD) on the plateau. There are three main serious altitude health problems. First, high altitude pulmonary edema (HAPE). A high incidence is observed between newcomers to high altitude and lower incidence of HAPE after reascent of Tibetans are quite different with reports from North America and from the Andes. Second, high altitude heart disease (HAHD). The infants and children are especially at risk. Most infants affected by this disease are from Han origin, and presented severe congestive cardiac failure due to pulmonary hypertension few months after birth or after arrival to high altitude. Autopsies show right ventricular hypertrophy and muscular thickening of peripheral pulmonary arteries. The average mortality was 15%, so that infantile HAHD is a fatal disease. Third, Monge's disease or chronic mountain sickness (CMS). 15 patients with CMS in indigenous Tibetans were observed during 1991-1993. Pathophysiological studies were performed. Both epidemiological and clinical investigative data show that CMS exists on the Qinghai-Tibetan plateau.

Key Words: High altitude, Tibetan, Hen, Heart disease, edema, Monge's disease.

RESUMEN. En China, las altiplnicies de Qinghai en el Tibet son las más altas del mundo, y en ellas residen los Tibetianos nativos y los inmigrantes chinos (Han). Este artículo se ocupa de los problemas de las enfermedades producidas por la altura. Existen tres problemas serios producidos por la altura. Primero, el edema pulmonar de altura (HAPE); se observa una alta incidencia de HAPE en los recién llegados a la altura, y por el contrario una menor incidencia en los nativos de altura que reascienden a ella, lo que difiere con los reportes en Norte América y en los Andes. Segundo, la enfermedad cardiaca de altura (HAHD). Los niños y los infantes son los que se encuentran especialmente en riesgo. La mayoría de infantes afectados por esta enfermedad son de origin Han, y presentan insuficiencia cardiaca congestiva severa debido a hipertensión pulmonar dentro de los pocos meses de nacido o del arribo a la altura. Las autopsias muestran una hipertrofia ventricular derecha y un engrosamiento de la muscular de las arterias pulmonares periféricas. La mortalidad en promedio fue del 15%, tal que la HAHD infantil es una enfermedad fatal. Tercero, la enfermedad de Monge o Mal de Montaña Crónico (CMS). En los indígenas Tibetanos se han observado 15 casos de CMS entre 1991-1993. Los datos epidemiológicos y clínicos muestran que la CMS existe en la altiplanicie de Qinghai-Tibet.

Palabras claves: altura, Tibet, Hen, Enfermedad cardiaca, edema, Enfermedad de Monge.

INTRODUCTION

In China there are many high mountains and plateaus, and one of the most famous is Qinghai-Tibetan plateau, the so called "Roof of the world" because it is the world's highest and largest plateau, with an average elevation of more than 4,000 meters, it covers about 2'500,000 Km^2, which means one fourth the China's total area, and it plays a specific role in the national defense and in the economic development of China. The significance and importance of high altitude medical research in China are therefore selfevident.

The Qinghai-Tibetan plateau has a population of approximately ten millions inhabitants. Every year many hundred of thousands of people travel from low to highlands in this region, in fact, such large movement of populations from low plains to high altitudes has only occurred in Tibet. Therefore, how to provide medical advice to highlanders on how to maintain their health and strengthen their physical capacity is an important task for Chinese high-altitude medical researchers.

Based on the longer period of previous studies, it is clear that human and animals ascend-

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ing to, or those living permanently at high altitude are two groups with different biological status. We believed that a different biological models as well different physiological adaptive form exists in different populations. There is some evidence (Moore et al, 1992; Wu et al, 1994) that the Tibetan natives are better adapted to high altitude, and the Chinese Han immigrants are susceptible to the hypobaric hypoxia of high altitude. In fact, Han immigrants to the Tibetan plateau have to face the potential danger of high altitude disease. This paper deals with questions concerning HAD on the Qinghai-Tibetan plateau.

HIGH ALTITUDE DISEASE IN CHINA

The classification of HAD in China

The nomenclature of HAD in China differs some what from that used in the Western literature. For instance, in China mountain sickness is named "high altitude disease". Moreover, the classification of HAD based on the pathophysiology and clinical manifestation of illness seen at high altitude probably represents the current concept of altitude scientists in Qinghai-Tibet in general.

The terminology and classification of HAD in China is summarized as follows:

Acute High Altitude Disease (AHAD)
- Acute Mild Altitude Disease (AMAD)
- High Altitude Pulmonary Edema (HAPE)
- High Altitude Cerebral Edema (HACE)

Chronic High Altitude Disease (CHAD)
- High Altitude Deterioration HADT)
- High Altitude Heart Disease (HAHD)
- High Altitude Polycythemia (HAPC)
- Monge's disease or Chronic Mountain Sickness (CMS), also named "Mixed Form" of CHAD.

Among the various forms of HAD, there are three main serious altitude health problems, ie, HAPE, HAHD and CMS.

High Altitude Pulmonary Edema

The observations on the Qinghai-Tibetan plateau suggest the existence of two types of HAPE. The first type (Type 1, or ascent HAPE) afflicts lowland residents visiting high altitude above 3000 m (Wu and Li, 1989). The second type (Type 2, or reascent HAPE) affects persons living permanently at high altitude as well as high altitude natives after a sojourn at lower altitudes longer than seven days and subsequent reascent to areas above 3500 m (Wu et al, 1991).

In recent years, we have performed an epidemiological study of AHAD and HAPE on the tibetean plateau. Studies were carried out in three high altitude regions, a mountain area (Tanggula range, altitude 4,550 m), a pastural county (Madou, altitude 4,280 m) and a mining area (Muli, altitude 3,790-4,200 m).

The number of people visiting the Tibetan mountain areas resulting in an unique opportunity of contrasting the incidence of AMAD (AMS) and HAPE in newcomers to high altitude with that in Tibetan native who return to highland after visiting lowlands. For example, the Qinghai-Tibet Highway stretches from Xining (2261 m) to Lhasa (3658 m), covering a distance of 1937 km at an average altitude of 3500 m above sea level. Particularly, the section between Mt Kunlun and the Tanggula Range is situated permanently frozen earth above 4460-5200 m and is 500 km long. It has long been recognized as a dangerous road for tourists. Nevertheless, each year, about 120,000-150,000 of sojourners travel over this highway for visiting, pilgrimage or business purposes. Many adults with their children going back and forth between low and high altitude travel the road by buses. We recently performed a survey for AHAD at the rescue station of Tuo-Tuo river near the highway at 4,550 m, where most sojourners stay overnight. For this purpose, 5,355 adults and 464 children from both sexes were studied.

Madou county is a pasture-region situated near the source of Yellow's river at an elevation of 4,280 m above sea level. It has a resident population of 20,400 and approximately 92% of the

native Tibetan population is engaged in pasturing activities. Only four percent of Tibetan natives travel to low altitude each year, but is more than 5000 tourists visited annually. From these, 635 travellers who ascend the elevation for first time, and 1,720 Tibetan native residents who return to high altitude were included in the survey.

Muli is a mining community located on the Mt. Qulian at altitude between 3,790 and 4,300 m. A total of 602 newcomers of miners and their families from the plain areas to Muli during the 18 months of this study. The clinical observations were performed at the Madou county Hospital and the Muli mining Hospital.

In the present study, the diagnosis of AMS was based on history describing arrival at high altitude, and measured by an established symptom score derived from a questionnaire and physical examinations (Hackett et al, 1976; Maggiorini et al, 1990). The diagnosis of HAPE was based on radiographic criteria. The percentage incidence of HAPE is shown in Table 1.

Table 1.- Incidence of high altitude pulmonary edema in adults and children occurred on the Qinghai-Tibetan plateau.

Area	Altitude (m)	Subjects	Incidence (%)	Variety
Muli	3790-4200	602 newcomers	0.50	Type 1
Madou	4280	635 travellers	1.10	Type 1
		1720 Tibetans	0.17	Type 2
Tanggula	4550	5355 sojourners	1.27	Type 1
		464 children	1.51	Type 1
		1180 workers*	1.61	Type 1
		1638 Tibetans	0.24	Type 2

*Workers of constructing roads.

In Tuo-Tuo river of Tanggula ranges, the incidence of AMAD (AMS) and HAPE in adults was 38.2% and 1.27% as compared with 34.1% and 1.51% respectively in children. There was not statistically significant difference between adults and children ($P>0.05$). These data would suggest that lowland children are not more susceptible to AMS and HAPE than adults (Wu et al, 1987).

The incidence of 0.5-1.61% of HAPE in adults on the Tibet is in agreement with other reports in various altitudes and mountain areas of the world (Hackett et al, 1980; Hultgren, 1978; Menon, 1965).

The incidence of reascent HAPE on the Tibet was lower than those observed in South and North America. The incidence of reascent HAPE was reckoned to be as high as 6.1% by Hultgren and Marticorena (1978) in La Oroya (3750 m) in the Central Peru and 0.3-0.6% by Scoggin (1977) in Leadville, Colorado at 3100 m. The reasons for the differences are not clear, but it could reflect differences in the travel and the length of time to reascent from lowland to high altitude places. First, as La Oroya residents usually go to sea level, they travel to a lower altitude. In fact, many of the Tibetan residents did not go to sea level but usually they do to intermediate altitude such as Xining (2261 m), Lanchou (1800 m) or Xian (720 m). In addition, in Qinghai-Tibet, people who return to high altitude after a sojourn at a low altitude, travel only by railway or highway, from low altitude,they reach their altitude home in about 2 to 4 days. In contrast, in La Oroya, dwellers travel by modern highway only for a few hours. On the other hand, the severe HAPE was more common in children than in adults in Peru (Hultgren et al, 1961), but in Tibet, Tibetan children rarely travel to sea level because of the labour style and the economic condition.

In conclusion, HAPE is a serious health problem for high altitude dwellers in Tibet, but further epidemiological and pathogenesis studies are still needed.

High Altitude Heart Disease

Although Anand and Chandrawshekhar (1992) stated that the syndrome of sub-acute mountain sickness (SAMS) has only recently been described in man, in fact this illness was described in the Qinghai-Tibetan plateau by Chinese scientists earlier. It was first reported by Wu and Liu (1955). They described a Han (Chinese) infant girl aged 11 months born at Lhasa (3658 m) presenting dyspnoea, cyanosis and congestive cardiac failure.

At necropsy, marked right ventricular hypertrophy and muscular thickning of peripheral pulmonary arteries were found. The pathology ruled out the diagnosis of congenital and other organic heart disease, of these, the authors named the disease as: "High Altitude Heart Disease" (HAHD). Subsequently other similar cases were reported in Qinghai-Tibet. Now in China more is known about this syndrome (Wu and Lin, 1978; Wu et al, 1992).

Early clinical manifestations of HAHD were restlessness, nocturnal crying, sleeplessness, anorexia, coughing, polyhidrosis and hoarseness. During the attack of the illness,the patient presented with breathlessness, dyspnoea, cyanosis of the lips and fingers, and right-sided heart failure occurred (Lin and Wu, 1974). ECG and chest X-ray confirmed the presence of cardiac enlargement and dilatation of the pulmonary trunk. Echocardiography revealed significant right ventricular hypertrophy and dilatation in all studies. Right heart catheterization was performed in 7 cases during the onset of HAHD. The mean values for systolic, diastolic and mean pressure in the pulmonary artery were 68 ± 9.6 mm Hg (9.06 ± 1.28 KPa), 39 ± 7.8 mm Hg (5.2 ± 1.04 KPa) and 54 ± 8.2 mm Hg (7.2 ± 1.09 KPa), a degree of pulmonary hypertension two to three times greater than that corresponding to healthy children on the Tibet at the same altitudes. Necropsies were performed in 68 fatal cases (Lin and Wu, 1974; Li et al, 1966; Wu and Liu, 1955; Wu and Lin, 1978). The most significant pathological feature was the hypertrophy of the smooth muscle of the pulmonary arteries and arterioles. It thus seems clear that HAHD is the same illness as SAMS. In regard to the nature of HAHD, Wu et al (1965) were the first to propose that HAHD is a human model of Brisket disease in the cattle, which agrees with the recent view of Anand and Chandrawshekhar (1992). However, there are some special characteristics of HAHD observed in Qinghai-Tibet.

As a consequence of the rich accumulation of epidemiological and clinical data, we have strong evidence that HAHD has no age limit, and cases have been described in infants, children (Lin and Wu, 1974; Wu et al, 1965) as well as adults (Wu et al, 1965); the highest incidence ocurre in infants (89.5% of all the cases) (Lin and Wu, 1974). Most infants and children afflicted by this illness were of Han origin. There are three conditions in the occurrence of HAHD among children of Tibet (Lin and Wu, 1974; Wu and Liu, 1955; Wu and Lin, 1978). 1) Infants born at high altitude and remaining there since birth (account for 73.3%); 2) Infants born at low altitude and later brought up high altitude (16.1%); and 3) Children with their parents who migrated from an intermediate altitude to a higher altitude (10.2%). It is interesting to note that HAHD is rare in Tibetan native children and that a high degree of tolerance to hypoxia was shown in them, indicating that Tibetan children may be better adapted to high altitude, possibly due to a genetic adaptation.

On the contrary, some Han infants do not attain acclimatization even at moderate altitude. An epidemiological survey (Wu et al, 1983) showed that at altitudes between 2261-2808 m, the prevalence of HAHD was still 0.47% in Han children whereas there were no adult victims. At higher altitudes between 3050 and 5188 m, the prevalence of HAHD in children and adults appears to be 0.96% and 0.31% respectively, the former being significantly higher than the latter ($P<0.001$) (Wu, 1994). These data again suggest that susceptibility to HAHD is higher in children than in adults. Why are children more at risk than adults?. It is possible that at high altitude, children may have a more reactive pulmonary vascular reaction to hypoxia, the foetal structure of the pulmonary arterial tree resulting from increased pulmonary hypertension, may remain as a chronic condition after birth and may contribute to the development of HAHD in children.

In some of the pediatric patients the symptoms improved following treatment with oxygen, cardiotonics, diuretics and corticoids. HAHD can also be relieved by descent. However, sometimes the progress of the illness is so rapid than even descent cannot prevent a fatal outcome. In this malignant type, as well as the later stage of the illness, even when patients are brought down to hospitals at 2261 m, mortality is higher than 62%.

Since the average mortality for hospitalization was 15% (Wu et al, 1987), infantile HAHD seems to be a serious and potentially fatal disease. Finally, HAHD occurs on the Qinghai-Tibetan plateau offers a very important and timely problem to be investigated.

Chronic Mountain Sickness

Chronic mountain sickness (CMS) or Monge's disease is commonly described in Leadville, Colorado, and Cerro de Pasco, Peru (Winslow and Monge, 1987). On the Tibet, most of our patients with CMS are chinese Han immigrants, and the average length of stay at high altitude is over 10 years. Apparently, CMS occurrence among Tibetan natives residing on the Tibetan plateau has not been detailed; speculation is rife about this, the problem remains to be clarified.

Based on our previous investigations, we suggested that in some native Tibetans, after living for many years above altitude of about 4000 m, lose their acclimatization and develop CMS (Wu et al, 1992). During 1991-1993, we observed 15 cases of CMS occurred in indigenous Tibetans in Tibet. The mean age of the patients was 44.8 years with a range of 36-62 years. All patients were male, the resident elevation was between 3,719 m and 4,280 m above sea level. The diagnosis of CMS was confirmed by the clinical symptoms, physical examination and laboratory studies. The physiological parameters were compared with the healthy Tibetans, who were matched for age, sex, occupation and comparable elevation of residence.. The clinical and physiological characteristics of the cases of CMS in Tibetan natives were listed in Table 2.

As seen in Table 2, severe hypoxemia, excessive polycythemia, accentuated pulmonary hypertension, marked right ventricular hypertrophy and blunted peripheral chemoreceptors characterized the Tibetan patients who had CMS. The criteria for the diagnosis used by the physicians of our Institute are similar to those customarily described (Winslow and Monge, 1987). Thus, we were able to obtain a reliable diagnosis of CMS in the Tibetan natives.

Table 2.- Comparison of the physiological parameters between CMS in Tibetan natives and healthy Tibetans (M±SD).

	CMS (n=15)	Healthy Tibetans (n=20)	P value
Mean age (year)	44.8±8.2	40.4±5.7	NS
Hb (g/dl)	23.2±1.4	15.6±2.2	0.01
Hct (%)	75.3±9.4	58.6±4.8	0.01
PaO_2 (KPa)	5.6±0.6	6.7±0.6	0.01
HVR	Blunt	Normal	
2,3-DPG (umol/ml RBC)	5.1±0.8	4.5±0.6	0.05
PAM (KPa)	5.3±2.1	3.2±0.6	0.01
Right Ventricular hypertrophy	Marked*	None or Mild	
Congestive Hearth Failure	in 4 cases	None	

Hct: Hematocrit; HVR: Hypoxic Ventilation Response; 2,3-DPG: 2,3-Diphosphoglycerate;PAM: Mean Pulmonary Arterial Pressure. *Marked in all cases.

As indicated in the introduction, the Tibetans, who have lived at high altitude longer than other populations on the earth, have ample opportunities to adapt to hypoxia. Nevertheless, why are some persons of the Tibetan group suffering from CMS?. We attributed this to the following reasons. First, despite the fact that Tibetan population may be better adapted to high altitude, a few susceptible individuals may remain in the population. Second, the elevation of residence in some nomads Tibetan were as high as over 4,500-5,000 m above sea level, especially in the summer time, the pasture-grounds were always higher than 5,000 m. In addition, tibetan persons with heavy exertion for a long periods, or persons suffering from respiratory infections, or any other factors of increasing hypoxia, could be more liable to suffer from CMS. nswered questions yet to be investigated.

In any event both clinical and physiopathological data suggest that CMS (Monge's disease) exist in the Qinghai-Tibetan plateau. CMS occurrence among Tibetan natives residing in Tibet is of immense practical application, since it is clear that Monge's disease is a syndrome which represents a loss of acclimatization to high altitude.

In conclusion, the Qinghai-Tibetan plateau and its width, height, climate, topography and the various ethnic populations are not entirely similar to the other high altitude areas of the world. Therefore, in the field of high altitude medicine and physiology, comparative studies of populations who have lived at different altitude areas for varying lengths of time are needed. On the other hand, the Qinghai-Tibetan plateau is an optimal testing place for high altitude researchers. Tibet now, the mysterious land has a strong appeal to altitude scientists all over the world.

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