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Kashin-Beck disease and iodine deficiency in Tibet

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Abstract We evaluated iodine and selenium status in 575 children between 5 and 15 years with Kashin-Beck disease from endemic and non-endemic areas. Of these 267 (46%) children had goiter. The proportion of subjects with goiter was higher in the villages with Kashin-Beck disease than in the control village. In the villages with Kashin-Beck disease, 105 (23%) of the subjects had a serum thyrotropin greater than 10 mU/l as compared with 3 (4%) in the control village. The percentages of low serum thyroxine values and low serum tri-iodothyronine were greater in the villages where Kashin-Beck disease was endemic than in the control village. The percentages of low urinary iodine concentration were significantly greater in the subjects with Kashin-Beck disease. The results suggest that in areas where severe selenium deficiency is endemic, iodine deficiency is a risk factor for Kashin-Beck disease.

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Résumé Nous avons étudié le statut en iode et en sélénium chez 575 sujets Tibétains âgés de 5 à 15 ans affectés par la maladie de Kashin-Beck; 267 (46%) sujets avaient un goitre. La proportion de sujets avec goitre était plus importante dans les villages où la maladie de Kashin-Beck était endémique que dans le village contrôle. Le nombre de sujets avec une thyrotrophine sérique supérieure à 10 mU/l était de 105 (23%) dans les villages où la maladie de Kashin-Beck était endémique et de 3 (4%) dans le village contrôle. La proportion de valeurs basses de thyroxine et tri-iodothyronine sérique était plus grande dans les villages où la maladie de Kashin-Beck était endémique. La proportion de valeurs basses en iode urinaire était significativement plus grande chez les sujets présentant la maladie de Kashin-Beck. Ces résultats suggèrent que dans les régions où la carence endémique en sélénium est sévère, la carence en iode soit un facteur de risque pour la maladie de Kashin-Beck.

Introduction

Kashin-Beck disease is an osteoarthropathy of uncertain aetiology that is endemic in areas of China, Siberia and North Korea where selenium deficiency is also endemic [9]. Affected patients have a variable degree of joint deformation together with limitation of joint mobility. Osteoarthropathy usually becomes evident in patients aged between 5 and 15 years.

The disorder has been reported in white migrants to the endemic areas, and clinical and radiological improvement occurs in children who move to non-endemic areas [1, 10]. Selenium deficiency has been suggested as a risk factor because selenium concentrations in the serum of individuals living in areas where the disease is endemic are lower than the respective values in non-endemic areas [11, 12].

In China, endemic selenium deficiency is closely related to endemic iodine deficiency, but the converse is not true [7]. However, as hypothyroidism impairs skeletal development in children [5], it is possible that iodine

Table 1 Characteristic findings in subjects with and without Kashin-Beck disease living in endemic and non-endemic villages. T4 se-thyroxine, T3 tri-iodothyronine, TBG se-thyroxine-binding globulin, TSH thyrotropin, Gpx se-glutathione peroxidase)

Characteristics	Subjects with kbd in villages with kbd	Subjects without kbd in villages with kbd	Subjects without kbd in control village	P
Age in years (no.)	10±3 (280)	9±3 (222)	9±3 (73)	<0.001
Male sex in % (no.)	62 (173)	42 (94)	52 (38)	<0.001
Skeletal delay in years (no.)	2.6±1.3	2.6±1.4 (196)	2.4±1.3 (71)	NS
Height for age as Z score (no.)	-3.2±1.0	-3.2±1.4 (218)	-3.1±1.0 (73)	NS
Goiter prevalence rate in % (no.)	49 (136)	52 (115)	22 (16)	0.001
Serum T4 <6 µg/dl in % (no.)	31 (262)	27 (201)	11 (72)	0.004
Serum T3 <150 ng/dl in % (no.)	38 (257)	29 (201)	19 (72)	0.005
Serum TBG <18 mg/l in % (no.)	45 (268)	25 (204)	19 (72)	<0.001
Serum TSH >10 mU/l in % (no.)	23 (262)	22 (202)	4 (72)	0.001
Urinary iodine <1 µg/dl in % (no.)	36 (273)	25 (212)	14 (72)	<0.001
Serum selenium <5 ng/ml in % (no.)	35 (265)	43 (201)	31 (55)	NS
Serum Gpx <100 U/l in % (no.)	23 (207)	29 (147)	0 (63)	<0.001

deficiency and Kashin-Beck disease might be associated. Therefore we assessed the iodine and selenium status of Tibetans with Kashin-Beck disease.

Materials and methods

In May 1995 we conducted a survey in Lhasa Prefecture, Tibet, of 11 villages where Kashin-Beck disease was reported by the health authorities and in one where it was not.

Clinical examination was performed, and blood samples were collected for measurement of serum selenium by atomic-absorption spectrometry. Serum glutathione peroxidase activity (Gpx) was measured spectrophotometrically, and serum thyroxine (T4), triiodothyronine (T3) and thyrotropin (TSH) by chemiluminescence detection. Serum thyroxine-binding globulin (TBG) was measured by radioimmunoassay [8]. A sample of urine was collected to measure the iodine content using a Technicon Auto Analyser [8]. Radiographs of the right hand and foot were taken.

The geometric means (-1 SD, +1 SD) were recorded for serum thyrotropin, selenium, glutathione peroxidase and urinary iodine because the long-transformed values fit a normal distribution better than the un-transformed values. The results were analysed by one-way analysis of variance, and by the chi-square tests.

Results

The individuals studied were divided into three groups: those with Kashin-Beck disease, those without Kashin-Beck disease from endemic villages, and those from the control village (Table 1). In the 11 villages where Kashin-Beck disease was endemic, 575 children (49%) had this disease. Details of the results are given in Table 1 from which it can be seen that males were affected more frequently than females ($P < 0.001$) and the mean age was higher in the Kashin-Beck disease group. The proportion of individuals with delayed bone age and growth retardation was similar in the three groups. Among all the 575 individuals, 267 (46%) had a goiter. The proportion of individuals with a goiter was higher in the villages with Kashin-Beck disease than in the control village. In the villages with Kashin-Beck disease, 105 (23%) had a serum thyrotropin greater than 10 mU/l as compared to three (4%) in the control village. The percentage of low

serum thyroxine values and low serum tri-iodothyronine was greater in individuals from the villages with Kashin-Beck disease than in those of the control village. The proportion of low serum thyroxine-binding globulin was greater in individuals with Kashin-Beck disease than in those free of the disease in the same village or in individuals in the control village. The proportion of low urinary iodine concentration was significantly greater in those with Kashin-Beck disease than in the two other groups. Serum selenium concentrations and Gpx were low in all three groups, but in children from the control village no values of Gpx fell below the quartile of Gpx values (100 U/l).

Discussion

The low serum selenium concentrations and the low serum glutathione peroxidase activity illustrate the severity of selenium deficiency in Tibet as glutathione peroxidase is a selenium-containing enzyme, and measurements of serum glutathione peroxidase are a marker of selenium status [6].

The geographical association between Kashin-Beck disease and selenium deficiency was first reported in the 1970s [1]. However, Kashin-Beck disease does not occur in every selenium-deficient area in China and so far selenium deficiency alone has not been demonstrated to cause any disease. Even Keshan disease, a selenium-responsive cardiomyopathy endemic in China, is not fully explained by a low selenium status [2]. As far as individual subjects are concerned and in the severely selenium-deficient group that we studied, there was no direct evidence of selenium status as a risk factor for Kashin-Beck disease. Other environmental factors such as oxidative stress due to mycotoxins contaminating cereals might play a role [3].

Hypothyroidism secondary to iodine deficiency was found significantly more often in the villages affected by Kashin-Beck disease than in the control village. The greater frequency of low values of serum thyroxine-binding globulin concentrations in individuals affected

by Kashin-Beck disease could be accounted for by protein-energy malnutrition. Hypothyroidism in children results in epiphyseal dysgenesis, delay of osseous development and reduced enchondral ossification, and this probably contributes to the clinical features of Kashin-Beck disease in Tibet.

Kashin-Beck disease and iodine-deficiency disorders remain major public health problems in rural Tibet [8]. However, the effect of selenium deficiency on Kashin-Beck disease remains to be established. If selenium supplementation proves effective, it will remain important to correct first any iodine deficiency in order to avoid aggravating hypothyroidism [4].

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