Rickets in China

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China is a developing country located in the temperate zone. Its mainland extends approximately from 20° to 53° northern latitude. In 1988 China had a large population of 1.08 billion, with almost 300 million children under the age of 14. About 20 million infants are born each year. The country has a low per capita income but in the last ten years, through a policy of openness to the outside world, its economic development has been steady and rapid.

China has always paid great attention to child health work, with emphasis on prevention and treatment of common diseases (1). Among those, rickets is prevalent in infants and young children. Besides its adverse effect on growth and development, it lowers general body immune resistance, predisposing children to many diseases. A small number of patients may sustain permanent chest or lower extremity deformities. Therefore, much attention has always been given to rickets.

In the last few years, the epidemiology of rickets in China has been clarified and large scale preventive and therapeutic measures taken. In many districts, the incidence of the disease has been lowered and for the country as a whole, severe cases and permanent deformities have significantly decreased.

Rickets may be roughly divided into two large groups, i.e., rickets due to vitamin D deficiency and rickets due to other causes. The latter group comprises several entities discussed elsewhere in this book but is collectively very small in number and no different in China from what is seen in other countries.

This chapter deals only with rickets due to vitamin D deficiency.

EPIDEMIOLOGY

Incidence

A nationwide survey was carried out from 1977 to 1983 (2). Altogether, 184,901 children under the age of three were examined and 75,259 cases of rickets diagnosed, with an overall incidence of 40.7% (Table 1).

In Northern China, the highest incidence was in Inner Mongolia, at 87.1% and the lowest in Tianjin, at 20%. In Central China, the highest incidence was in Shan-
TABLE 1. Incidence of rickets in Chinese children under 3 years of age (1977–1983)

<table>
<thead>
<tr>
<th>Districts</th>
<th>No. of children examined</th>
<th>No. of rickets</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern China</td>
<td>103,439</td>
<td>51,086</td>
<td>49.4</td>
</tr>
<tr>
<td>Central China</td>
<td>48,395</td>
<td>16,024</td>
<td>33.1</td>
</tr>
<tr>
<td>Southern China</td>
<td>33,067</td>
<td>8,149</td>
<td>24.6</td>
</tr>
<tr>
<td>Total</td>
<td>184,901</td>
<td>75,259</td>
<td>40.7</td>
</tr>
</tbody>
</table>

dong, at 62.7% and the lowest in Shanghai, at 13.1%, while in Southern China the highest was in Guizhou, at 38.4% and the lowest in Guangzhou, at 16.2%. These figures show that rickets is a common disease in children throughout the whole of China, being more common in the North than in the South.

There are two main reasons for this high incidence: inadequate exposure to sunlight and limited use of vitamin D supplements; doctors are highly alert and may err on the side of over-diagnosis.

Relevant Factors

Age

Rickets is more common in infants under one year of age: about 40–80% in Northern China and 30–60% in Southern China. It is even more common in low-birthweight infants. After the first year, the incidence gradually lowers and more cases are in the convalescent stage. In Northern China, most cases are mild or moderately severe, while in Southern China, most cases are mild.

Season

The incidence and severity of rickets is obviously related to the adequacy of exposure to sunlight. In Northern China, the incidence of rickets is higher and the disease more active in the winter months, while in the summer months, the incidence is lower and more convalescent cases are seen. In Southern China, where the weather rarely gets cold enough to interfere much with outdoor activities, the seasonal difference is not obvious.

Urban Versus Rural Areas

In most districts, the incidence of rickets is higher in the rural than in the urban areas. Although air pollution and high-rise buildings are more common in the cities, urban people are more educated, make better use of the sunlight, and have easier access to vitamin D preparations.
Feeding

The incidence of rickets is lower in breast-fed infants compared to bottle-fed infants. Those infants and young children who feed on carbohydrates rich in phytate or oxalate have a higher incidence of rickets because these compounds interfere with calcium absorption.

Other Diseases

Rickets predisposes patients to bronchitis, pneumonia, and diarrhea, and increases the severity and duration of these diseases.

DIAGNOSIS

It is based on the history, clinical manifestations, blood chemical changes, and x-ray findings.

In early cases, many patients have psycho-neural symptoms, such as irritability, frightening spells at night, and excessive perspiration. As a result of rubbing of the head against the pillow, occipital alopecia is frequent. These features are non-specific and may occur in other diseases. But in an infant with vitamin D deficiency, they are early manifestations of active rickets, often appearing before definite biochemical or x-ray changes.

The bone changes are more specific. Craniotabes is more common in young infants; rosary and Harrison’s groove occur in older infants; bow legs and knock-knees will only appear at weight-bearing, after one year of age.

Biochemical serum changes manifested by low calcium, low phosphorus, and elevated alkaline phosphatase are present in the more advanced cases.

Typical x-ray changes of the bones are diagnostic but they usually appear later than the other changes.

As shown by many authors, serum 25-hydroxyvitamin D levels are very helpful in the diagnosis, especially in early cases. Low levels are a definite sign of vitamin D deficiency and an indication for giving vitamin D. However, it is often normal in rachitic patients who have recently been given vitamin D or who have had significant exposure to sunlight before blood examination.

Clinically, rickets is classified in China according to (i) stage of development: early, advanced, healing, and sequelae; and (ii) severity of disease: mild, moderately severe, and severe.

Congenital Rickets

Congenital rickets has been reported in Northern China (3). The incidence is about 5–30% higher in infants born late in the cold season. The infant’s mother is usually
deficient in vitamin D, as established by low 25-hydroxyvitamin D levels. Sporadic cases have also been seen in Southern China.

Clinical Manifestations

Symptoms and signs are usually not striking during the newborn period. Large fontanels, wide sagittal suture, and craniotabes are suggestive but they may also occur in normal newborns. Some patients may have a rosary or pigeon breast deformity.

Blood Chemistry

Low serum phosphorus, low serum calcium, and high serum alkaline phosphatase may be found but not as regularly as in rickets of older infants.

X-Ray Changes

Typical x-ray manifestations of rickets are: (i) the provisional zone of calcification in the metaphysis is blurred, brushlike, or invisible; and (ii) the metaphysis is concave or cup-like. These changes are more obvious in the tibia.

Late-Onset Rickets

Rickets is most common in infants and young children but if vitamin D deficiency exists, it may occur at any age, especially during the adolescent period when growth is rapid. Investigations carried out in several districts in Northern China showed that the incidence of rickets in adolescent children is about 5–15%, and higher in the latter part of the cold season (4).

Symptoms

There are three main groups of symptoms: general weakness—general fatigue and weakness of lower extremities are common. The patients trip and fall down easily when walking or running; leg pain which occurs mainly in the knees, more severe when weight-carrying, walking downstairs, or running. Leg pain disappears when the patient is sitting or lying down.

Other symptoms: Patients often have dizziness, insomnia, and excessive perspiration. Numbness of the hands and feet, and spasms of the fingers and toes may also occur. There is no swelling or limitation of movements of the knee joints. Obvious bow leg or knock-knee deformities may appear within a few months. Some-
times, beading of the costochondral junctions (rosary) and flaring of the costal margins are present.

**Laboratory Findings**

Serum phosphorus and calcium are usually lower than normal, Ca x P being less than 36. Serum alkaline phosphatases are elevated. Urinary calcium is very low.

**X-Ray Changes**

In early cases, bone changes are not obvious. In advanced cases, there is fraying and widening of the metaphyses, and cortical thinning and osteopenia along the diaphyses.

**Diagnosis**

In the early stage, it is often missed unless this disease is kept in mind. In children with the above-mentioned symptoms and history of vitamin D deficiency, the diagnosis should be seriously considered. Blood chemical studies are helpful. Deformities of the legs, if present, should lead to the diagnosis. In contrast with vitamin D resistant cases, the patient's growth and development are normal, since onset is usually during adolescence, and response to ordinary doses of vitamin D is favorable.

**TREATMENT (5–7)**

Mild rickets often recovers spontaneously after adequate exposure to sunlight in the summer season. However, once rickets is diagnosed, vitamin D therapy should always be implemented.

For early rickets, 5,000 to 10,000 IU are given daily by mouth for one month followed by 500 IU daily. Alternatively, 200,000 to 300,000 IU are given intramuscularly for one to two doses at a one-month interval.

Many Chinese doctors like to use large intramuscular doses because they do not depend on the parents for daily administration, they are not affected by the intestinal absorption status, and they have a quicker and more potent effect. Doses as large as 600,000 IU intramuscularly, three times at weekly intervals have been recommended in a pediatric textbook for medical students (8). However, the advisability of using such large doses at such short intervals has recently been questioned by some Chinese doctors. If no improvement is seen three months after starting the treatment, detailed studies should be carried out. When a large single dose is used, most doctors would give calcium for three days beforehand to avoid a possible, although rare, hypocalcemic tetany.
HYPERVITAMINOSIS D

With the doses detailed above, cases of hypervitaminosis D have been encountered. The usual symptoms are anorexia, irritability, and restlessness. Some patients may have nausea, vomiting, and diarrhea or constipation. In severe cases polydipsia and frequent urination are frequent. A few children died of renal calcification and subsequent failure. The symptoms are non-specific and diagnosis may be much delayed unless this condition is kept in mind and a detailed history of vitamin D intake obtained. In acute over-dosage, hypercalcemia is more common, while in chronic over-dosage, x-ray evidence is more prominent.

It is interesting to note that although doses many times larger than the normal requirement have been commonly used in the treatment, cases of hypervitaminosis D have been surprisingly few, possibly because of the normal feed-back mechanisms which prevent serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D from rising to very high levels.

Most cases of intoxication occur after very big doses, usually over 2.5 million IU given over a period of a few weeks or months. If the diagnosis is made in time and the patients are treated properly including the use of corticosteroids, almost all the cases recover unless calcification of the kidneys or other vital organs have occurred.

To prevent hypervitaminosis D, it is important to let the parents know that too much vitamin D may be harmful to the child and all doctors should obtain a detailed history of vitamin D intake before further vitamin D medication is given.

A few patients have anorexia, nausea, vomiting, and diarrhea only after one or two doses of vitamin D (total dose less than 300,000 IU), without biochemical or x-ray changes. The symptoms disappear quickly after discontinuation of vitamin D. These cases are considered to be hypersensitive to vitamin D.

PREVENTION (5,6,7)

To prevent rickets, attention should be given to vitamin D supplementation of pregnant women and children from birth to adolescence. This important notion should be included in the health education of the people. Outdoor activities with direct or indirect exposure to sunlight is to be encouraged and supervised.

During the last trimester of pregnancy, when fetal growth is rapid, and especially in the cold season, 100,000 to 200,000 of vitamin D are given intramuscularly or orally in single or divided doses. Extra calcium intake is advised.

All infants with low birthweight, artificially-fed or born in the winter season are given vitamin D. It is started 1 to 2 weeks after birth. A daily dose of 400 to 800 IU is given orally but not many parents can be depended upon to give it regularly. Preferably, 50,000 to 100,000 IU are given in a single dose intramuscularly or orally once a month up to one year of age, except during the summer months. The same total dose has been divided and given at weekly intervals with equally good results.

If no monthly medication has been used, it is advised to give a single dose of
200,000 IU intramuscularly or orally to infants in Northern China and 100,000 IU to infants in Southern China during the cold season. If necessary, a second dose may be given. In general, no calcium supplement is necessary. This program, called “vitamin D during cold season and sunshine during hot season” is relatively simple and effective. It is easier to carry out on a large scale.

Vitamin D fortified milk has been used in some cities with good results in artificially-fed infants.

Attention should also be given to vitamin D status during the adolescent period. Early diagnosis and treatment will result in complete recovery. Delayed action may result in permanent deformities.

REFERENCES


DISCUSSION

Dr. Markestad: Are long term rachitic deformities common in China? On repeated inquiries I have been told by obstetricians and orthopedic surgeons in Libya that they do not see permanent pelvic or other skeletal deformities from rickets indicating that rickets for a large part is a self-limiting disease. With the high incidence figures from China, including a substantial number of congenital rickets, I would expect a high incidence of late sequelae.

Dr. Zhou: Considering the number of rachitic patients we have, sequelae, such as bow legs, knock-knees, pigeon breast, are extremely uncommon. Women with deformed pelvis are also not common.

Dr. Guesry: I was very interested by the figure that you showed of the large number of babies suffering from rickets in your country. You said that you have a program to prevent rickets but I think distributing vitamin D throughout the country should be an enormous task. Could you tell us a bit more how it is organized, what kind of vitamin D is distributed, how it is distributed?

Dr. Zhou: The national survey, of course, showed the magnitude of the problem. In certain districts, we have given intramuscular large doses of vitamin D on a wide scale and the result was a marked decrease in the number of rickets. But we know that this must be a continuous problem because we are having 20 million infants born every year. Considering our present financial situation, we have difficulty to cover such a large population on a continuous basis. We encourage exposure to sunlight for prevention.

Dr. Arnaud: Can you establish a correlation between the enormous number of rickets that you see and the incidence of postmenopausal bone loss and osteoporosis in China?
Dr. Zhou: I am not impressed by the magnitude of the osteoporosis problem. I don't think it is more common than in any other country.

Dr. Mautalen: Are the criteria to make the diagnosis of rickets just clinical or also include x-ray changes?

Dr. Zhou: The diagnosis is based on clinical plus either biochemical or radiological evidence, but when we say early cases the radiological evidence may be just suggestive. Some radiologists will call it rickets while other radiologists will say it is not. We cannot wait until all evidence is very clear cut, because then those would be very late cases.

Dr. Elidrissy: It was my impression that in a country like China the problem of rickets could be solved not by vitamin D supplementation but, more simply, by exposing people to the sun. With the level of organization in China this should be easier than supplementing a huge population.

Dr. Zhou: Unfortunately, in a large part of the country, the latitude and the prolonged cold season are real problems, so we cannot make more use of the sunshine and we have no other choice but to resort to vitamin D supplementation in these areas, which is a difficult task to fulfill.

Dr. David: You said that you use intramuscular injections of vitamin D as a preventive measure. In my opinion it is costly, painful and, considering the large number of infants concerned, it probably causes some complications related to the intramuscular injection itself. So why do you use it? In France, like in your country, we don't have any milk or food enrichment with vitamin D and prevention of rickets is done through systematic oral administration of vitamin D. The majority of the infants receive daily oral doses, but when poor compliance is suspected the prevention is done by oral administration of single large doses every 3 to 6 months. They are administered at the district welfare center at the time of the free periodic consultations, very often in parallel with a vaccination. I can assure you that it is very efficient and I would therefore suggest that you preferentially use the oral route which is safer, cheaper, and as efficient as the intramuscular one.

Dr. Zhou: I agree with your suggestion. Poor compliance and possible incomplete absorption if given by the oral route are the main reasons for injection.

Dr. Senterre: I am very surprised at the marked incidence of congenital rickets in the northern part of China. Could it be a question of the terms we use to define congenital rickets? Have you personally seen in a stillborn baby x-ray signs of rickets?

Dr. Zhou: All the cases of congenital rickets are diagnosed on the basis of x-ray evidence, soon after birth and not later. In the original studies, the authors made these x-ray examinations together with histological examinations on babies who died before or soon after birth to be sure that the x-ray image reflects the change in the bone. Of course we cannot study histologically all the congenital rickets cases because the majority do not die, and we have to rely on the x-ray evidence.

Dr. Senterre: Do you explain all those cases by low maternal 25(OH)D levels?

Dr. Zhou: Patient's mothers usually have low 25(OH) vitamin D values. When it was measured, it was also low in the newborn infants.

Dr. Marx: I think the reason that intermittent high doses of vitamin D may be particularly effective for the prevention of treatment of vitamin D deficiency is that, even at high doses, vitamin D is well absorbed, like other sterols. Being insoluble in water, the absorbed vitamin D is distributed rapidly and efficiently into body fat, which presents a reservoir of infinite capacity. The stored vitamin D has a biological half-life of greater than 30 days. From storage pools a small fraction is released back into blood each day to be activated, degraded, or returned to storage pools. Thus a single oral dose, in fact, established a form of "depot
therapy" that can be sufficient for many months. On a different aspect of the problem, total or partial alopecia is a clear feature in hereditary resistance to 1,25(OH)₂D. We think this reflects loss of a trophic role of 1,25(OH)₂D in all hair follicles. This seems different from the occipital alopecia you described in nutritional vitamin D deficiency; what is the cause of this occipital alopecia?

Dr. Zhou: Rachitic children are hyper-irritable. They shake their heads back and forth, rubbing against the pillow; after a while practically all the hair in that region is rubbed off. We call it "pillow alopecia."

Dr. Glorieux: About 80% of the Chinese population is rural. Do you have a breakdown of your data comparing rural communities versus large urban centers to see whether the reported incidence corresponds to these different ways of life?

Dr. Zhou: This varies from one province to another. In general the incidence in the urban area is lower than in the rural area. But in certain provinces, it is the reverse. So the difference is not that great.

Dr. David: I have the impression from the discussion that is going on concerning occipital alopecia that rickets may be overdiagnosed in your country through the use of isolated non-specific clinical signs. This could explain your surprisingly high incidence of rickets. I have frequently seen infants or children being considered as having rickets and being treated with vitamin D on the basis of isolated signs which are simply benign morphological or developmental variants like for example frontal bossing, bowing of the legs, minor thoracic dystrophy as pectus excavatum or pigeon chest, delayed walking or teething, or even simply fatigue. This is probably not a medical practice limited to my country. As far as occipital alopecia is concerned, this sign mainly indicates that the infant is lying on his back most of the time and needs to be stimulated. Certainly, when this is an isolated sign, it does not diagnose rickets.

Dr. Zhou: All our cases are diagnosed on the basis of symptoms plus certain biochemical changes, like elevated alkaline phosphatase, or suggestive radiological changes. Whenever a child presents psycho-neural symptoms suggestive of rickets, we are on the alert that the child may be having rickets and proceed with the necessary examination. Sometimes, of course, the doctors may just go ahead and treat.