X-linked hypophosphataemia in South Africa

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Objectives. To investigate the pattern of clinical presentation in a series of South African subjects with X-linked hypophosphataemia (XLH) with particular reference to ethnic differences in presentation and inheritance, and to determine the perceptions and psychosocial problems associated with the disease.

Design and setting. The clinical details of 50 subjects were collected from their records as well as from examining those currently attending the clinics held at Chris Hani Baragwanath Hospital and the National Health Laboratory Services in Johannesburg. There were 17 males and 33 females in the study. The psychosocial part of the study involved interviews with 20 parents and 7 subjects (aged 16 years or more).

Results. Thirty-one of the subjects were black, 17 white and 2 Indian. The mean age of clinical onset was 2.02 years (range 0.25 - 10 years). Fifty-four per cent of the cases were apparently sporadic. The prevalence of sporadic mutations was 64% among the black subjects and 41% among the white subjects. No differences were found in either clinical or biochemical presentation between genders or ethnic groups, despite an apparently higher sporadic presentation in the black children. The study also showed that this disorder had not only affected family life but also the lives of the subjects and their interpersonal relationships. The hereditary nature of the condition was not clear to most parents even after having attended the clinic for many years.

Conclusions. South African subjects with XLH have similar features to those reported in other studies but there is a higher prevalence of sporadic mutations in the black subjects. Better counselling services are needed to improve the understanding of this condition among parents of affected children.

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X-linked hypophosphataemia (XLH) is the commonest form of familial rachitic disease.[1] It was first described in 1937 by Albright *et al*.[2] who coined the term 'Hypophosphatemic vitamin D resistant rickets'. It is inherited as an X-linked-dominant trait with the mutant gene (PHEX) being located in the Xp22.1-22.2 region of the X chromosome.[3] The most striking clinical features of this disorder are growth retardation, lower limb deformities, hypophosphataemia, and a defect in renal tubular phosphate reabsorption.[4] Affected children generally have short stature and bowing of lower extremities, whereas adults may develop osteomalacia, dental disease, and osteo-arthritis. Although XLH is inherited as an X- linked condition, some 30% of cases are reported to be the result of sporadic mutations. The aims of this study were to investigate the pattern of clinical presentation in a series of South African XLH subjects with particular reference to ethnic differences, to assess the inheritance in each case, and lastly, to determine the perceptions and psychosocial problems associated with the disease.

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Methods

Subjects for the clinical part of the study included those who attended the clinic held at the Medical Research Council Mineral Metabolism Research Unit (MMRU) at Chris Hani Baragwanath Hospital as well as those who consulted the genetic counselling clinic of the Department of Human Genetics, National Health Laboratory Services (NHLS) in Johannesburg. Clinical details of the subjects were collected either from patient records, or from examination of those subjects who attended the clinic within the period of this study (January - December 1998). Altogether 50 subjects (17 males and 33 females) were investigated. Thirty-one of them were black, 17 white and 2 Indian. For the genetic part of the study, the family pedigrees of the subjects were derived from their records and family histories were taken from those who attended the clinic to verify their pedigrees. Routine biochemical investigations in serum (calcium, phosphorus, total alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), 25-hydroxy vitamin D (25-OHD) and 1,25-dihydroxy vitamin D (1,25$(OH)_2$D) and creatinine) and in urine (calcium, phosphorus and creatinine) were performed in the laboratory of either the MMRU or the NHLS. Subjects for the psychosocial part of the study included 20 parents who had a child with XLH, and 7 subjects (aged 16 years or more) who volunteered to participate. They were interviewed using a specially constructed schedule of 21 questions. In addition, a validated questionnaire on depression (Beck's Depression inventory)[5]

was used to assess depression in subjects. The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Chi-squared and Fisher's exact tests were used to analyse the data.

Results

The results of the clinical part of the study were collected from a retrospective analysis of the records available on the 50 subjects (17 males and 33 females) supported by clinical examination of 26 of those subjects during the study period. Analysis of the pedigrees of the subjects showed that the disorder was more common in females than males (the sex ratio was 2:1), as expected in X-linked-dominant conditions. The sporadic type of mutation (N = 27, 54%) was slightly but not significantly more common than the hereditary type (N = 23, 46%). However, sporadic cases tended to be more prevalent in the black (64%) than the white population (41%) (p = 0.11).

Most of the affected subjects had shown symptoms in early childhood and the mean age of onset of symptoms of XLH (according to the parents' reports) was 2.02 years, with a range of 0.25 - 10 years. However, the subjects with the hereditary type of XLH had a significantly earlier reported onset of the disorder (1.54 ± 0.85 years) than did those with the sporadic type (2.37 ± 1.75 years) (p = 0.03). The 17 white subjects also had a significantly earlier reported onset of the disorder (1.4 ± 0.66 years) than the 31 black subjects (2.37 ± 1.7 years) (p = 0.04).

The presenting clinical features were lower limb deformities (80%), short stature (10%), upper limb deformities (20%), rickety rosary (20%) and abnormal shape of skull (16%) (Table I).

The height for age z-score was significantly different between the black and white subjects, with white subjects (–2.39 ± 1.07) being taller than the black subjects (–3.79 ± 1.43). However, there was no difference between males and females, or between sporadic and hereditary cases. No significant racial or gender differences or differences between modes of inheritance were found for any biochemical test results (Table II). However, there was a trend for those with the inherited form of the disease and for whites to have higher serum calcium values (p = 0.09 and p = 0.07 respectively).

Table I. Physical deformities at the time of presentation(n = 50)

Physical deformities	Number of subjects before treatment: Number	% of total subjects
Lower extremeties		
Varus deformities	40	80
Valgus deformities	7	14
Joint abnormalities	4	8
Fracture of femur	2	4
Pelvic deformities	1	2
Ligamental laxity	1	2
Upper extremeties		
Widened wrist (splaying)	10	20
Varus deformity of elbow	1	2
Skull		
Abnormal shape (e.g. scapho-cephaly, brachycephaly)	8	16
Frontal bossing	4	8
Spinal deformities	1	2
Chest		
Rickety rosary	10	20
Harrison's sulcus	4	8

Table II. Biochemical findings (at presentation) in different XLH subgroups (mean ± SD)*

	Total	Sporadic	Inherited	p-value	Male	Female	p-value	Black	Caucasoid	p-value
Serum total calcium (mmol/l)	2.36 ± 0.14	2.31 ± 0.10 (22)	2.42 ± 0.15 (18)	0.09	2.33 ± 0.16 (15)	2.37 ± 0.12 (25)	0.37	2.33 ± 0.12 (28)	2.42 ± 0.15 (11)	0.07
Serum phos-phorus (mmol/l)	0.89 ± 0.20	0.88 ± 0.16 (22)	0.94 ± 0.23 (18)	0.20	0.88 ± 0.20 (15)	0.90 ± 0.20 (25)	0.72	0.89 ± 0.17 (28)	0.89 ± 0.27 (11)	0.99
Serum ALP (IU/l)	821 ± 397	816 ± 466 (23)	829 ± 298 (18)	0.92	785 ± 390 (15)	843 ± 407 (26)	0.65	836 ± 386 (29)	742 ± 431 (11)	0.51
TRP (%)	73.2 ± 19.6	70.0 ± 22.8 (16)	78.2 ± 12.1 (10)	0.30	71.9 ± 18.2 (10)	73.9 ± 20.9 (16)	0.80	†	†	†

*Numbers in parenthesis are the number of subjects included.
†Calculations were not done because there were very few results.
ALP = alkaline phosphatase; TRP = tubular resorption of phosphate.

The biochemical features were typical of subjects with XLH (normal serum calcium, hypophosphataemia, elevated serum ALP, and reduced tubular reabsorption of phosphate (TRP) and TmP/GFR (maximum rate of renal tubular reabsorption of phosphate per litre of glomerular filtration rate) (Table II).

In spite of medical treatment, 77.7% of the subjects required corrective orthopaedic surgery. Prolonged hospital admissions were also associated with this disorder. Only a few subjects had complications such as tertiary hyperparathyroidism (N = 1, 2%) and chronic diarrhoea (N = 4, 8%) associated with phosphate treatment. One subject had a foot drop following a corrective tibial osteotomy.

The data for the psychosocial part of the study were collected using a schedule of questions in an interview with the parents of 20 subjects and with 7 older subjects (aged 16 years or more). Analysis of the responses to the interview showed that parents did not have a clear understanding of the hereditary nature of XLH before attending a specialised clinic (Table III), and even after attending such a clinic it was still not clear to 50% of the parents. Before attending the clinic only 20% understood the hereditary nature of the disease. Forty-five per cent of subjects believed that nutritional causes and lack of sunlight were major contributing factors.

Table III. Parents' initial belief about the causes of XLH

Causes	Number	%
Heredity	4	20
Not heredity	13	65
Nutrition	6	30
Lack of sunlight	3	15
God	2	10
Witchcraft	1	5
Carrying the child on the back	1	5
Unknown	3	15
Total	20	100

In the present study, parents were asked if the disorder had any effect on the child's relationship with other children. Four parents (20%) reported that their children had problems with other children partly due to the physical deformity, inability to run and short stature associated with XLH. Although parents described various family problems, only 1 parent stated that her affected child had a difficult relationship with a sibling partly due to his physical deformities.

The majority of the parents (N = 17, 85%) stated that they would like to have prenatal diagnosis of XLH in future, but only a few of them (N = 2, 10%) would have requested termination of pregnancy on the basis of a positive result. Although XLH is not a life-threatening condition, it still affected the functioning and progress of the subjects and disrupted their lives (Table IV).

It was also associated with significantly more depression in mothers than fathers (p = 0.04). Altogether, 60% of the parents did not have contact with other affected families and 83% of these parents said that they would like such contact. Finally, most of the parents (90%) indicated that they would like to join a support group.

Table IV. Disruption of life of subjects as reported by themselves

Disruption of life	Number (%)
Unable to walk long distances	7 (100)
Regular intake of medicine	7 (100)
Regular visit to the hospital	5 (71.4)
Unable to work	3 (42.8)
Prolonged hospitalisation	3 (42.8)
Short stature	3 (42.8)
Unable to go to school	2 (28.6)
Unattractive appearance	1 (14.2)

Discussion

In the cohort there were more females (66%) than males (34%), as is to be expected in an X-linked-dominant disorder like XLH. Although the male-to-female ratio in the sporadic cases was lower (1:1.7) than in the subjects with a family history (1:2.3), there was no statistically significant difference between the two groups. Sporadic cases were more common in black (20/31, 64%) than in white subjects (7/17, 41%), but no statistically significant difference was found (p = 0.11).

The mean age of onset of XLH in the subjects studied was 2.02 years. This is similar to the age of onset reported by Carpenter.[6] In the present study, the subjects with the inherited type of XLH had a significantly earlier age of reported onset of the disorder than did those with the sporadic type. Also, the white subjects had a significantly earlier age of reported onset of the disorder than did the black subjects. One possible explanation is that white subjects might have been identified earlier than black subjects because of better health awareness and accessibility of health services (which in the past were more easily available to the former group). No differences were found when the age of onset in male and female subjects was compared.

Although many presented for treatment several years after the onset of symptoms, 5 parents (who had XLH themselves) brought their newborn children for assessment. For the whole group, the mean age of presentation for diagnosis was 4.65 years, with a range of 0.01 - 16 years. The remaining 18 parents, who were XLH subjects themselves, did not bring their children for a check-up immediately after birth, but rather waited till their children started showing features of XLH, such as bowing of the legs. This was probably because of lack of knowledge of the hereditary nature of the condition, and indicates that parents should be made aware of this aspect of XLH and the possible implications for their children.

No significant difference in age of presentation was found between males and females, black and white subjects or between those with hereditary and sporadic forms of XLH. This is similar to the findings of the study conducted by Whyte *et al*.[4] in 1996, who found no difference in age of presentation between male and female, black and white or hereditary and sporadic form of XLH.

The findings of the present study showed that the main presenting complaints were bowing of the legs (88%), problems in walking (16%), and short stature (10%). Obviously these problems motivated the parents to seek medical attention. Abnormalities of the upper extremities are uncommon[7] and were found only in 2 (4%) of the cases in the present study. Econs *et al*.[8] mentioned other clinical features such as bone pain, dental abscess, and abnormalities of the skull (e.g. scaphocephaly). Dental manifestations in XLH are usually reported in older children and adult subjects with XLH.[9,10] In the present study, dental problems were present in 8% of the subjects.

A problem of continuing concern for children with XLH is that most of them never achieve normal height. However, several investigators have found that normal growth can be maintained for long periods through appropriate medical management.[1,6,11] Clinical examination of the subjects in the present study showed that 52% were below the 5th percentile of height for age at the time of presentation. Although their height improved after 1 year of treatment, it was still below normal. Although the height *z*-scores were significantly lower in black than in white subjects ($p < 0.01$), there was no difference in height *z*-scores between the male and female subjects and those with the hereditary and sporadic forms of XLH. Explanations for higher height *z*-score in white subjects are: (*i*) that white subjects seek treatment earlier and are more compliant with treatment because of greater familiarity with medicines and more accessible health services; and (*ii*) in general white subjects are taller than black subjects because of better socio-economic and nutritional circumstances.

In the present study, serum phosphorus, TRP and TmP/GFR values were significantly lower than normal at presentation, as expected in XLH subjects. Statistical analysis showed that mean serum iPTH and 25-OHD values of the subjects at presentation were no different from normal. Circulating $1,25(OH)_2D$ levels were also normal in subjects with XLH but inappropriately so given the ambient hypophosphataemia, which normally serves to increase circulating levels of this metabolite.[11] In this study, statistical analysis showed that mean $1,25(OH)_2D$ levels of the subjects before onset of treatment were no different from normal ($p = 0.77$). Whyte *et al*.[4] failed to show any evidence that the sex or ethnicity of the subjects affected the expression of the gene for XLH. They used data for height, dietary calcium, and numerous biochemical parameters. They also compared these parameters in subjects with hereditary or sporadic forms of XLH but found no differences. They concluded that XLH is a sex-dominated disorder without any gene dose effect. Similarly, in the present study no differences in biochemistry (serum calcium (total and ionised), magnesium, phosphate, ALP, iPTH, TRP and TmP/GFR) were found between the male and female or black and white subjects or between those with the hereditary or sporadic forms of XLH. However, the relatively small numbers of subjects in each subgroup made statistical testing unreliable.

Treatment of XLH aims to correct the hypophosphataemia, improve growth, and reduce the severity of the bone deformities and resulting limitations on activity. At present, combined therapy with phosphate and calcitriol or $1\alpha\text{-OHD}_3$ is the best approach.[1,12] The majority of subjects in the present study were treated with phosphate supplementation and the vitamin D analogue, $1\alpha\text{-OHD}_3$. However, poor compliance (57.5%) with the treatment regimen was a major problem, particularly in school-going children and subjects from remote areas. Problems were aggravated by the non-availability of medicine (as phosphate and $1\alpha\text{-OHD}_3$ were not on the Essential Drug List) in hospitals without any specialists. The subjects had to come to an academic hospital to collect the medicine every month, which presented a major stumbling block. Only the very few subjects who had medical aid coverage could afford to get a regular supply of medicine without attending an academic hospital. The subjects with XLH were usually seen at the MMRU clinics once every 3 - 6 months. As a result, it was not possible to monitor subjects regularly. Inclusion of the two drugs necessary for treatment on the Essential Drug List might be helpful in increasing their availability in remote areas. The situation is even more hopeless for subjects outside South Africa, where these drugs are not available. In this study, 77.7% of the subjects had to undergo corrective orthopaedic surgery partly because of these problems.

The sporadic type of XLH accounted for 54% of the cases in this study. However it may be difficult in an X-linked condition to determine whether an isolated case represents a new mutation or whether the mother has inactivation of an X chromosome carrying the defective gene and a functioning normal X chromosome. It is therefore problematic to decide what the *a priori* risk is for an isolated case, which may have resulted from a new mutation or from being transmitted by an apparently non-affected mother, and what the recurrence risks for the mother's future children are. In future, molecular studies might be helpful in this situation.

The findings of this study showed that most of the parents did not have a clear understanding of the hereditary nature of the condition before attending a specialised clinic at MMRU or NHLS. However, even after attending a clinic, this was still not clear to 50% of the parents. In a study in the USA, Econs *et al*.[8] found that despite the presence of XLH in family members,

most of the affected individuals had little or no knowledge of the disease. They concluded that the lack of parental knowledge might be due to their limited access to medical care, forgetting that they had been told the diagnosis, or the physician's failure to make the diagnosis of the disease. These explanations may also be valid for the subjects in the present study. In addition, the lack of genetic counselling services accessible to the subjects and lack of proper referral to available services might play a role in this regard.

XLH is not a lethal condition and therefore affected children live with their chronic physical disabilities in the community. The psychosocial issues, which are associated with chronic disabilities, would in general apply to XLH. The deformities associated with XLH and possible stigmatisation of affected people should be taken into consideration when counselling subjects and their families.

The majority of the parents (75%) said that the physical deformities of their children had caused disruption in their lives and 8 parents (40%) said that their children had problems at schools. The physical deformities of the children had also caused disruption in family life. Some problems were associated with financial issues, such as the need for transport, and loss of parental income as the child had to be taken to hospital regularly. Others were associated with disruption of family dynamics caused by prolonged hospitalisation of the affected child and the necessary regular visits to hospital. These problems should be taken into account when planning intervention programmes for the management of chronic disorders such as XLH. However, for people facing a future with the challenge of a physical disability, the pattern of progression of disability over time may be of significance in the development of psychological distress.[13] It is necessary to evaluate the quality of life of subjects with XLH by assessing their material circumstances, and interpersonal and personal psychosocial wellbeing, so that a better counselling service and intervention programme for subjects with XLH and their families can be provided.

Although the nature and severity of a disabling condition are not the sole determinants of family functioning, the presence of a disabled child has a significant effect on family members. This should be taken into consideration while counselling parents with a child with XLH, and it may be beneficial to counsel the whole family instead of only one or two members.

In the present study, 4 parents (20%) reported that their children had problems with other children partly due to the physical deformity, inability to run and short stature associated with XLH. These problems could probably be ameliorated by educating parents and teachers about XLH.

No study has investigated the psycho-social aspects of XLH on adult subjects. As subjects grow older, their paediatricians usually stop treating them and they are taken care of by other medical practitioners who may not be aware of the problems associated with XLH subjects. Children with chronic physical handicaps have been found to be at risk for psychological and social adjustment problems as they grow older. Role modelling by successful disabled adults and counselling may assist in successful transition to adulthood. Also, accurately identifying in a timely manner those physically handicapped children who are functioning at clinically significant levels of maladjustment may aid in preventing further psychosocial morbidity.[14,15]

The majority of the older subjects interviewed said that they knew about the hereditary nature of the condition and that they could pass on the disorder to their children. This knowledge might be helpful when they have their own children.

In view of these findings, referral for proper genetic counselling is necessary for these parents and the older subjects, and the establishment of a support group should be considered.

Conclusion

The findings show that South African subjects with XLH have similar features to the patients in other studies, but there is a higher prevalence of sporadic mutations in black subjects. Better counselling and/or referral to both general and genetic counselling services is needed to improve the understanding of this condition and its inherited nature and reduce psychosocial effects among the parents of affected children.

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