

X-LINKED HYPOPHOSPHATEMIA IN A SOUTH AFRICAN POPULATION

Debashis Basu

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Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree
of Master of Science in Medicine in Human Genetics

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DECLARATION

I, Debashis Basu declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in Human Genetics at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

30 day of July, 1999

To
My parents Ranendra Kumar Basu and Subhra Basu,
my sister Debjani Basu and
my wife Jayati Basu

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

PUBLICATION

1. Basu, D., Pettifor, J.M., Kromberg, J.G.R. X-linked hypophosphatemia in a South African population. S Afr Med J, vol. 89. no. 4, Endocrinology, Metabolism and Diabetes issue, pp. 471.

PRESENTATIONS

1. Basu, D., Kromberg, J.G.R. and Pettifor, J.M. X-linked hypophosphatemia in a South African population- a psychosocial study. Oral Presentation at the 8th Biennial Southern African Human Genetics Congress, Cape Town, South Africa 9th to 12th March 1999.
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ABSTRACT

X-linked Hypophosphatemia (XLH) is the most common form of familial rachitic disease. 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. The most striking features of this disorder are growth retardation, lower limb deformities, hypophosphatemia, and a defect in renal tubular phosphate reabsorption. Although XLH is inherited as an X linked condition, some 30% of cases appear to be the result of sporadic mutations.

The aims of this study were to investigate a series of South African XLH patients, to describe the pattern of their clinical presentation, with particular attention to ethnic differences and response to therapy, to assess the inheritance in each case, and lastly, to determine the perceptions and psychosocial problems associated with the disease.

The subjects for the clinical section of the study were those who attended the Mineral Metabolism Research Unit (MMRU) clinic at Chris Hani Baragwanath Hospital and Johannesburg Hospital as well as those who consulted the genetic counselling clinic of the Department of Human Genetics, SAIMR (South African Institute for Medical Research). The clinical details were collected from the subjects' records, and the examination of those subjects who attended the MMRU clinic during the period of this study. Altogether 50 patients (17 males and 33 females) were investigated. Thirty-one of them were black, 17 white and 2 Indian. For the genetic section of the study, the family pedigrees of the subjects were derived from their records and a family history was taken from those who attended the clinic to verify their pedigrees. The subjects for the psychosocial section of the study were 20 parents with a child with XLH and seven patients (16 years or older) who volunteered to participate. They were interviewed using a specially constructed schedule of questions.

The findings of the clinical study showed that the main clinical problems of the patients were deformities of the lower and upper extremities, skull and chest, and short stature. Dental and hearing problems were present in a few cases. Radiological features suggestive of rickets in the children and osteomalacia (in two adult cases) were found. Most of the patients with

medical treatment (phosphate and 1α -dihydroxyvitamin D₃) and surgery, although compliance with treatment was a major problem.

The findings of the genetic study showed that hereditary cases occurred slightly more often than the sporadic cases in the series of patients studied. The female to male ratio in this study was nearly 2:1 as expected in an X-linked dominant disorder. Sporadic cases tended to be more common in black patients than white patients, although no statistically significant difference was found between the two groups. The patients with hereditary forms of XLH and white patients in general had a significantly earlier age of onset than did those with sporadic forms and black patients, respectively. The comparison of the results from blood biochemistry values and radiological examinations at the time of presentation showed that there was no evidence for effects of sex, race or form of mutations (sporadic or hereditary) on XLH gene expression. However, white subjects tended to be taller than black subjects were.

The results obtained from the psychosocial study showed that the parents were not fully aware of the hereditary nature of XLH even after attending clinics for many years. The presence of a child with XLH had not only affected the family dynamics, social activities and interpersonal relationships, but XLH had also affected the life and social activities of the patients themselves. The findings of the present study showed that parents appreciate genetic counselling, and therefore, this service should be better utilised. A parent support group should be initiated for the essential support that can be provided only by a peer group. Information regarding XLH should be made available to the public to raise awareness.

Further research needs to be conducted to study the long term effect of the disorder in adults, to investigate the usefulness of screening of infants born to patients with XLH, to investigate the nature the PHEX gene, and then using molecular studies, to ascertain the actual number of sporadic and hereditary cases, and the type of mutations in different population groups. Better counselling services are needed to improve the understanding of this condition among the parents of the affected children. It is also necessary to do long term follow up of XLH patients, so that their needs can be met and they can live their lives to the best of their potential.

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LIST OF ABBREVIATIONS

1 α -OHD ₃	1 α -dihydroxyvitamin D ₃ or Alfa-calcidiol
1,25-(OH) ₂ D ₃	1,25-dihydroxy-vitamin D ₃ or Cacitriol
25-OHD ₃	25-hydroxy vitamin D ₃
ALP	Total alkaline phosphatase
BMD	Bone Mineral Density
BMI	Body mass index
Ca	Calcium
Ca/Cr	Ratio of calcium (mmol/l) and creatinine (mmol/l) in urine
CI	Confidence interval
DXA	Dual energy X-ray absorpiometry
GH	Growth hormone
Gy mice	Gyro mice, (murine model of XLH)
<i>Hyp</i> mice	Hypophosphatemic mice (murine model of XLH)
IGF-1	Insulin like growth factor-1
Mg	Magnesium
MMRU	Mineral Metabolism Research Unit
PCR	Polymerase Chain Reaction
Pex	Murine homologue of PHEX gene
PEX gene	Previous nomenclature of PHEX gene
PHEX gene	Phosphate regulating gene with homologies to endopeptidases on the X chromosome
Pi	Phosphate
PTH	Parathyroid hormone
RT/PCR	Reverse transcriptase/ Polymerase Chain Reaction
R _x	Treatment
SAIMR	South African Institute for Medical Research
SD	Standard deviation
TmP/GFR	Renal threshold phosphate concentration (also denoted as the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate)
TOP	Termination of pregnancy
TRP	Tubular reabsorption of phosphate
XLH	X-linked Hypophosphatemia

CHAPTER 1

INTRODUCTION

X-linked hypophosphatemia is a genetic condition causing physical deformities in affected persons. It also induces psychological and psychosocial problems for persons with XLH and his or her family. This introductory chapter will cover the nature of rickets and X-linked hypophosphatemia (XLH) in particular, the motivation for this project, and its aims and objectives.

1.1 INTRODUCTION

Rickets is a general term used to describe the histopathological and radiological changes resulting from a group of diverse metabolic disorders. The condition presents in children as a result of failure of or delay in mineralisation of the growth plate of the growing bones. Ancient descriptions of rickets have been found in the writings of Homer (900 BC) and Soranus Ephesius (130 AD). Much later Daniel Whistler (1645) and Francis Gilson (1650) provided detailed descriptions of the disease. It was described as a disease, which occurred in young children producing severe and often fatal deformities (Pettifor and Daniels, 1997).

There are number of different causes of rickets, which can be broadly divided into two groups: Calcium deficiency rickets, and Phosphorus deficiency rickets (Pettifor, 1998).

Calcium deficiency rickets results from an inadequate supply of calcium, which can occur due to (a) abnormalities in vitamin D metabolism or (b) a diet deficient in calcium. The characteristic biochemical features of calcium deficiency rickets are hypocalcemia, and elevated parathyroid and alkaline phosphatase concentrations. Globally this type remains the most frequent form of rickets. However, the incidence of this form of rickets has been almost eradicated in a number of developed countries, as a result of fortification of foods with vitamin D and the use of vitamin D supplements in at risk groups (Pettifor, 1998).

This group also contains some inherited form of rickets associated with abnormalities of vitamin D metabolism. Vitamin D dependency rickets (type I) is an autosomal recessive disorder associated with mutations in the 1- α -hydroxylase gene. Hereditary vitamin D resistant rickets or vitamin D dependency rickets (type II) is also an autosomal recessive disorder and it is caused by the mutation in the vitamin D receptor gene. (Pettifor, 1998).

Phosphorus deficiency rickets results from phosphorus depletion despite an adequate vitamin D intake. Unlike calcium or vitamin D deficiency, it is not associated with secondary hyperparathyroidism (Glorieux, 1996). It may occur due to the following: (a) decreased intake of phosphorus, (b) decreased intestinal absorption of phosphorus, and (c) increased renal losses of phosphate (Pettifor, 1998).

The average diet usually contains more than enough phosphorus to meet the daily requirements. However, inadequate intake of phosphorus may occur, for example, in breast fed premature infants.

Unlike calcium, phosphorus absorption in the intestine is only partially controlled by body needs, and is generally very efficient. However, phosphorus absorption can be inhibited by the ingestion of phosphorus binding agents e.g. aluminium hydroxide (Glorieux, 1996).

Phosphate excretion by the kidney is controlled mainly in the proximal tubule. There are several conditions characterised by either single or multiple tubular ion transport defects, leading to decreased phosphorus reabsorption, e.g. XLH, Fanconi's syndrome (Pettifor, 1998).

1.2 BACKGROUND OF THE STUDY

X linked Hypophosphatemia is the most common form of familial rachitic disease (Rasmussen and Tenenhouse, 1994). It is usually inherited as an X linked dominant trait with the mutant gene being located in the distal part of the short arm of the X chromosome: hence it is now referred to as X linked hypophosphatemia (XLH)

(Glorieux, 1996). The incidence of XLH has been estimated, to be between 1 in 10000 and 1 in 100000, and 1 per 20000 seems to be the most widely quoted figure (Rasmussen, et al., 1994). The incidence of XLH in South Africa is not known. However, the condition is found in people of all ethnic groups. To date, no study has reported the role of ethnicity in the clinical presentation of the disorder.

XLH is associated with an abnormality of renal tubular phosphate reabsorption. The three most striking features of this disorder are growth retardation, lower limb deformities, and hypophosphatemia (Whyte, Scranck, and Armamento-Villareal, 1996).

Recently, mutations of the PHEX gene (Phosphate regulating gene with homologies to endopeptidases on the X chromosome) have been found to be associated with XLH and it may therefore soon become possible to offer molecular testing and diagnosis (Dixon, Christie and Wooding, et al., 1998).

XLH is associated with clinical as well as psychological and psychosocial problems for the affected persons and his or her family. Being a parent of the handicapped child is not a role people choose for themselves (Garguilo, 1985). Therefore, the unprepared parents of children with XLH have to cope with the physical and emotional problems associated with their children having this condition. As XLH is a genetic disorder, the psychosocial burden on the patients and their families could be comparable to that found in other genetic disorders (McCollum and Silverburg, 1979). However, very few studies on families with a child with XLH and on the dynamics in these families have been reported in the literature, and therefore the researcher was interested in pursuing this aspect of the condition.

1.3 MOTIVATION FOR THE STUDY

This study was initiated due to the fact that there was a number of patients with XLH attending the clinics of the Mineral Metabolism Research Unit (MMRU) at Chris Hani Baragwanath Hospital and Johannesburg Hospital and the genetic counselling clinics at the Department of Human Genetics, School of Pathology, South African Institute for Medical Research (SAIMR). Many of these families had not been fully

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investigated or properly documented.

With the availability of new diagnostic techniques and the improved understanding of this disorder, it is now possible to diagnose XLH quite easily by a clinical examination, blood and urine tests, and radiological examination. Use of regular appropriate treatment started from an early age may reduce the incidence and severity of the bone deformities that occur in untreated patients.

It was therefore decided that a group of patients with XLH in South Africa should be studied and their history and clinical findings documented. Also an assessment of any ethnic differences in inheritance and clinical presentation could be undertaken and the psychosocial problems associated with XLH could be described. The outcome of such a study should be the improvement of the service for patients with XLH and their families.

1.4 AIMS AND OBJECTIVES

The broad aim of this study was to investigate a series of patients with XLH regarding their clinical presentation and their perceptions of the disease and psychosocial problems related to the disease. This study consisted of two parts, a retrospective and a prospective part and three sections: a clinical, genetic and psychosocial section. The aims of these three sections were as follows:

- (a). Clinical study. To determine in a South African group of subjects with XLH:
1. the clinical picture (e.g. anthropometric measurements, deformities)
 2. the changes in biochemical parameters over time e.g. serum calcium (Ca), phosphorus, total alkaline phosphatase (ALP), intact parathyroid hormone (PTH), tubular reabsorption of phosphate (TRP), renal threshold phosphate concentration (also denoted as T_{mp}/GFR , the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate) and urinary calcium/creatinine ratio (Ca/Cr), at diagnosis and during treatment
 3. the radiological features at diagnosis, and during treatment
 4. the prevalence of complications

(b) Genetic Study: To determine:

1. the family history
2. the prevalence of sporadic and hereditary types of XLH
3. the ethnic differences in presentation

(c). Psychosocial study. To investigate:

1. some of the psychosocial problems associated with XLH and the level of depression, attitudes, needs, and problems of parents with an affected child
2. attitudes towards prenatal diagnosis (if available, in future)
3. the perceptions and myths about the disorder

1.5 SUMMARY AND CONCLUSIONS

XLH is the most common form of familial rachitic disease but it has not been thoroughly studied in South Africa. A number of patients with XLH, who had attended the clinics at the MMRU and/or the SAIMR were available for study. They had not been fully investigated from the clinical, genetic, or psychosocial point of view. The availability of new diagnostic techniques and the improved understanding of this disorder have lead to better management of the affected patients and to prevention of the deformities that may occur in untreated patients. It was therefore decided that a group of patients with XLH in South Africa should be investigated, that their history and clinical findings, mode of inheritance of their disorder, and psychosocial problems should be properly documented. They could then be counselled more appropriately.

CHAPTER 2

REVIEW OF LITERATURE

In this chapter, relevant reports from the literature with regard to the nomenclature used in connection with XLH, the clinical description, biochemistry, radiology, management, genetics and psychosocial issues associated with XLH will be reviewed.

2.1 HISTORICAL DEVELOPMENTS

Initial descriptions of hypophosphatemic rickets emphasised the poor clinical response to vitamin D, rather than the distinctive findings of the marked hypophosphatemia, which is associated with the disorder. It was first described in 1937 by Albright, who coined the term 'Hypophosphatemic vitamin D resistant rickets' (Albright, Butler and Bloomberg, 1937; Winters, Graham and Williams, et al., 1958). In 1940, Christensen first reported the familial occurrence of the condition in a mother, her son and her daughter (Christensen, 1940). In 1959, it was established that the most uniform hallmark of this condition was not rickets but hypophosphatemia, secondary to renal phosphate wasting (Winters, et al., 1958; Graham, McFalls and Winters, 1959). When inheritance was analysed with hypophosphatemia as a genetic marker, an X-linked inheritance was recognised. These studies revealed that a single X-linked gene was sufficient to confer all the usual manifestations of the disease in some affected females, thus strongly suggesting X-linked dominant inheritance (Rasmussen and Anast, 1983). Therefore, the currently preferred terminology for hypophosphatemic rickets is X linked hypophosphatemia (XLH) or in some texts familial hypophosphatemic rickets, which describes the primary mineral disturbance and the mode of inheritance. These terms indicate the distinction between XLH and the true biochemical resistance to vitamin D (Glorieux, 1996).

2.2 CLINICAL DESCRIPTION OF XLH

2.2.1 PRESENTATION AND DIAGNOSIS

2.2.1.1 Clinical presentation

The mildest abnormality is purely biochemical: hypophosphatemia. Although low serum phosphorus is evident at birth, it is only at the time of weight bearing, that the leg deformities and the slow growth rate become sufficiently striking to attract attention and make parents seek a medical opinion (Latta, Hisano and Chan, 1993).

Children with XLH typically present with their first symptoms in the second or third year of life. However characteristic rachitic deformities of the distal femur generally start developing in patients with XLH by one year of age, although there is a considerable variation in severity (Carpenter, 1997). Lower extremities are almost always more extensively involved than upper extremities. The most common manifestations of XLH in children are short stature, bowing of lower extremities, and defective mineralisation of cartilaginous epiphyseal plates (rickets) with consequent slow growth and skeletal deformities (Orstavik, Orstavik and Halse, et al., 1996). Striking negative findings are lack of muscle weakness, tetany and convulsions, which are common features of other inherited forms of vitamin D resistant rickets (Rasmussen, et al., 1983). Other clinical presentations include bone pain, bone overgrowth at the sites of muscle attachments around joints, dental abscesses, enthesopathy (ligamentous calcification), and scaphocephaly (Econs, Samsa and Monger, et. al., 1994).

The most common manifestations in adult patients are defective mineralisation of the endosteal bones (osteomalacia), dental disease and osteoarthritis (Orstavik, et al., 1996). Affected females may require Caesarean section because of pelvic deformities (Miller, 1979). As the affected patients mature, pseudofractures, skeletal deformities, osteomalacic bone pain, progressive ankylosis and dental caries occur which can be alleviated and prevented by appropriate medical therapy (Orstavik, et al., 1996). Brendt and his colleagues (1996) studied the clinical course of hypophosphatemic rickets in 23 adults in Germany and found that the mean final height was

152.4 cm $\pm$ 8.5 SD (Standard Deviation) in females and 157.3 cm. $\pm$ 8.9 SD in males which were shorter than the respective national averages. Decreased joint mobility was found in all patients, and deviation of normal leg axis was observed in 18 patients, in spite of 23 corrective osteotomies in the past. Dental problems were found in 14 patients (Brendt, Ehrich and Lazovic, et al., 1996). However, the phenotypic features of the disease are variable and many of the above defects are of inconsistent severity and are not always apparent in all adult patients with XLH (Friedman, Lobaugh and Drezner, 1993).

Females with XLH appear to be less severely affected than males, probably due to the lyonization of one of the X chromosomes (Connor and Ferguson-Smith, 1997). However such an effect does not exist for renal phosphate reabsorption (Orstavik, et al., 1996). XLH is fully expressed in hemizygous male patients but females have a variable presentation. Some females, who are obligate carriers of XLH, have been described without any evidence of bone disease (Burnett, Dent and Harper, et al., 1991). However, Whyte, et al. (1996) investigated the potential genetic influences on XLH expressivity in prepubertal children, and found no evidence of genetic heterogeneity or for gender, race, anticipation, or parent of origin effects. In several families, isolated hypophosphatemia without rickets can be found in some heterozygous females. Thus this trait is considered as the marker for the mutation (Glorieux, 1996).

2.2.1.2 Growth and skeletal abnormalities

Significant concerns in the childhood management of XLH are short stature and the outcome of final height. The severity of growth impairment is variable but primarily relates to poor lower-extremity growths (Carpenter, 1997). Seikaly and Baum (1996) reported that this short stature was not related to growth hormone (GH) or Insulin like Growth Factor-I (IGF-I) secretory defect. When plasma phosphorus concentration is normal, growth rate and skeletal development is usually adequate (Rasmussen, et al., 1983). However, when hypophosphatemia appears, skeletal growth decreases and there is often some retardation of bone age. The two most striking changes are progressive bowing of lower extremities and marked rachitic changes at the distal femoral and proximal tibial metaphyses. A picture of skeletal deformities in a 9 year

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old black girl with XLH is shown in Fig 2.1. These changes are associated with an increasingly evident waddling gait and short stature. Patients with rickets of distal femoral and proximal tibial metaphyses may exhibit either genu varum or valgum. The growth failure is most manifest in the legs but in most severely affected individuals may also involve the upper segment. Once the epiphyses close, many patients with skeletal deformity and short stature do well with no specific therapy and they show no evidence of osteomalacia on radiological examination, although histological osteomalacia may be present (Rasmussen, et al., 1983).



FIGURE 2.1 Picture of a 9 year old black girl with XLH

In clinically affected adults, bone overgrowth at the site of major muscular attachments and around joints may cause significant limitations of motion, particularly in elbows, shoulders and hips. Such overgrowth within the spinal canal may produce symptomatic cord compression requiring surgical intervention (Williams and Winters, 1972).

In patients with XLH, the characteristic microscopic feature in biopsy specimens of both trabecular and cortical bone is osteomalacia. There is an increase in histomorphometric quantitation of unmineralised bone matrix or osteoid. However, total bone volume may be normal or elevated. Cellularity of bone is usually reduced but in patients who develop hyperparathyroidism as a result of therapy, increased cellular parameters of bone turnover (e.g., cell number, or osteoblastic or osteoclastic surface) may be present. Dynamic histomorphometry shows a lag in mineralisation time (Carpenter, 1997). The defective bone formation in XLH is thought to be linked to an intrinsic osteoblastic defect. The hypomineralised periosteocytic lesions are landmarks of XLH and they never completely disappear even after active mineralisation has been restored at the endosteal surfaces. It is speculated that the osteoblast shares, with the renal tubular cell, a gene product which would specifically affect phosphate transport, and in ancillary fashion 1,25-dihydroxyvitamin D₃ [calcitriol or 1,25-(OH)₂D₃] synthesis (Glorieux, 1996).

2.2.1.3 Dental abnormality

Dental manifestations in XLH have been frequently reported. The basic dental defect manifests in the dentine. Dental abnormalities such as spontaneous dental abscess and a defect in dentin maturation are common findings (Yamamoto, 1997). However, there is no enamel hypoplasia, as opposed to the findings in cases of hypocalcemic rickets (Seow, Needleman and Holm, 1995). The patients may present with dentine defects, not apparent on clinical examination, which may cause dental abscesses, and early decay in young adults. Attrition (wearing down) and exposure of the abnormally formed dentine accounted for the route of infection in the primary teeth, but the route of infection in the permanent teeth has remained unexplained (Hillman and Geurtsen, 1996). Taurodontism (or bulls teeth, characterised by large pulp chambers) of the

permanent teeth was found in the more severely affected male subjects (Seow, et al., 1995; Goodman, Gelbier and Bennett, et al., 1998).

2.2.1.4 Renal abnormality

In patients with XLH, the renal tubule does not appropriately reabsorb filtered phosphate, resulting in excessive urinary excretion of phosphate. Therefore the steady state of circulating phosphate concentration is low. Renal tubular abnormalities are generally limited to phosphate, although a modest defect in glucose transport has been described in some families with the disease (Rasmussen, et al., 1994). Renal tubular acidosis has been described as a concomitant renal abnormality but the defect seems to correct with phosphate supplementation. Bicarbonaturia may occur secondary to concomitant hyperparathyroidism which develops due to therapy. Abnormalities in the metabolism of vitamin D are characteristic of patients with XLH. In spite of low circulating phosphate level, $1,25\text{-(OH)}_2\text{D}_3$ levels are inappropriately normal (Carpenter, 1997).

2.2.1.5 Other abnormalities

Cardiovascular abnormalities such as hypertension and left ventricular hypertrophy can occur in XLH patients in association with hypercalcemia, hypercalciuria, nephrocalcinosis and hyperparathyroidism. Whether the cardiovascular abnormalities are primary effects of XLH or represent complications of the treatment is unclear. Therefore, patients with XLH should be closely monitored for the development of hypertension and left ventricular hypertrophy (Nehgme, Fahey and Smith, et al., 1997).

There are some rare abnormalities reported in XLH patients, e.g. ossification of ligamentum flava, spinal canal stenosis (Yamamoto and Onofrio, 1994; Ballanytyne and Findlay, 1996). The bone disease of XLH can involve the base of the cranium, precipitating development of the Chiari-malformation (Caldermeyer, Boaz and Wappner, et al., 1995) and associated syringomyelia (Kuether and Piatt, 1998). Caldermeyer, Smith and Edwards-Brown (1995) described a case of XLH with marked bone thickening causing narrowing of the optic canals resulting in bilateral

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optic atrophy. The subject also showed metastatic calcifications in the walls of the globes. Vera, Cure and Naso, et. al. (1997) reported a rare coincidence of XLH with paraplegia. XLH patients can present with a wide variety of rheumatic symptoms like sacroiliitis (Onur, Celiker and Cetin, 1997). Stratakis, Mitsiades and Sun, et al. (1995) reported a case of recurring giant cell lesion in a boy with XLH, which was probably due to subclinical hyperparathyroidism. Baroncelli, Bertelloni and Perri, et al. (1995) described a patient with XLH who also had Klinefelter's syndrome. The patient had a normal growth pattern unlike the typical body proportions seen in XLH.

2.2.2 BIOCHEMISTRY OF XLH

The major biochemical abnormality in XLH is hypophosphatemia and the mode of inheritance is best revealed by using hypophosphatemia as the genetic discriminant (Graham, et al., 1959). In XLH, a defect in renal tubular phosphate reabsorption has been well established (Scriver and Tenenhouse, 1992). Impaired regulation of $1,25-(OH)_2D_3$ is associated with the paradoxical occurrence of normal plasma concentrations of $1,25-(OH)_2D_3$, in the face of hypophosphatemia. Thus, it is postulated that the abnormality of vitamin D metabolism is secondary to the primary phosphate transport defect, and its consequences on intracellular phosphate economy (Whyte, et al., 1996).

An initial biochemical investigation of XLH should include determination of serum calcium, phosphorus, and alkaline phosphatase (ALP) activity. XLH is characterised by hypophosphatemia, normocalcemia, normal plasma levels of parathyroid hormone (PTH), and $1,25-(OH)_2D_3$, and renal phosphate wasting (Econs, et al., 1994). Therefore, the diagnosis depends on an accurate assessment of renal phosphate handling. A convenient approach is to obtain a 2 hour urine collection after a 4 hour or overnight fasting for determination of creatinine and phosphorus level. Then the tubular reabsorption of phosphate (TRP) can be calculated from urine and simultaneous blood values (usually sampled at the midpoint of the timed urine collection) as follows:

$$TRP\% = 1 - \frac{\text{Urine Phosphorus in mmol/l} \times \text{Serum Creatinine in mmol/l}}{\text{Serum Phosphorus in mmol/l} \times \text{Urine creatinine in mmol/l}} \times 100$$

The normal TRP in children is 85 to 95%. It is best to interpret this number in relation to the filtered phosphate, as deduced from the serum phosphorus value. A normogram can be used to determine the renal threshold phosphate concentration (also denoted as TmP/GFR, the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate) (Walton and Bijvoet, 1975). Normal values for TmP/GFR are age related. A low TmP/GFR in the setting of low serum phosphorus values documents the inappropriate phosphate losses characteristic of XLH (Carpenter, 1997).

In children with XLH, ALP activity is usually elevated, but usually less than the 10 to 15 fold elevation seen in the hereditary vitamin D resistant rickets. Adults with XLH may have normal ALP activity despite impressive osteomalacia. Thus monitoring ALP level is not a particularly sensitive indicator of response to therapy, particularly in adults (Carpenter, 1997).

Other laboratory investigations, which can be useful for further confirmation of the diagnosis, include measurements of PTH, the circulating 25-hydroxyvitamin D₃ (25-OHD₃) and 1,25-(OH)₂D₃ (Carpenter, 1997). Characteristically, 25-OHD₃ levels are normal in subjects with XLH, distinguishing the disorder from vitamin D deficiency (Haddad, Chyu and Hahn, et al., 1973; Carpenter, 1997). Circulating 1,25-(OH)₂D₃ levels are also normal in subjects with XLH but inappropriately so given the ambient hypophosphatemia, which normally serves to increase circulating levels of this metabolite (Glorieux, Marie and Pettifor, et al., 1980)

In children with XLH, Soliman and alSalmi (1997) found that they had no abnormality of GH secretion but improvement of their linear growth was associated with significant increase of circulating IGF-I concentration during treatment.

2.2.3 RADIOLOGY IN XLH

Rickets, manifesting as a bowing of legs or knock knee deformity, is the most prominent skeletal feature of the affected children. Radiologically, the picture is that of rickets, although the signs of secondary hyperparathyroidism are absent (Pettifor, 1998). Features characteristic of rickets are most apparent at the ends of long bones,

radiographically manifesting as flared metaphyses with frayed borders, which may develop a cupped configuration (see Fig 2.2). As bowing progresses and the child grows older, an asymmetric appearance of the growth plates may become evident such that the medial and lateral aspects of the growth plate manifest a differing severity of the abnormality. The asymmetry is attributed to differential effects of weight bearing forces through the epiphysis resulting from the bowing (Carpenter, 1997).

FIGURE 2.2 Radiograph of right knee joint of a patient with XLH taken before onset of treatment

Studies of bone mineral density (BMD) in XLH patients must be interpreted carefully with respect to the methodology used. Studies using absorptiometry techniques

suggested that BMD of the spine is normal or increased in patients with XLH. This finding might be partly related to the tendency of the affected individual to develop extra ossicles, osteophytes, and spinal stenosis (Reid, Murphy and Hardy, et al., 1991). Computed tomographic determination of cortical bone density has been found to be low in XLH patients, despite increased cortical area. These findings are entirely consistent with histologic findings of increased total bone volume, but with low mineral content per unit area of bone (Carpenter, 1997).

2.2.4 RELATED HYPOPHOSPHATEMIC DISORDERS

Poor dietary phosphate intake may be a cause of hypophosphatemic rickets in infancy, particularly in breast-fed premature infants. The use of fortified breast milk has markedly reduced the incidence of this problem. Inappropriate ingestion of phosphate-binding antacid preparations, resulting in poor intestinal phosphate absorption, may result in a similar syndrome (Carpenter, 1997).

Acquired forms of primary hypophosphatemic rickets have been described in African children, with onset between 4 and 7 years of age. Affected children may demonstrate serum ALP levels in a more elevated range than that typical for patients with XLH. Muscle weakness was described as more prominent in these patients than those seen in patients with XLH (Pettifor, Ross and Quirk, et al., 1986). Exogenous agents toxic to the renal tubule (e.g., ifosfamide) may result in generalised renal tubular dysfunction or Fanconi syndrome, in which phosphate wasting may occur (Carpenter, 1997).

Other inheritance patterns of primary hypophosphatemic rickets have also been described, including autosomal dominant and recessive inheritance (see Table 2.1). A mild form of autosomal dominant hypophosphatemia is named as hypophosphatemic bone disease. This disorder responds well to therapy with active vitamin D metabolites (Scriver, McDonald and Reade, et al., 1977). In patients with autosomal recessive hereditary hypophosphatemic rickets with hypercalcuria, renal tubular phosphate handling is impaired but the appropriate physiological response of the

vitamin D 1 α -hydroxylase to hypophosphatemia remains intact. The disorder responds to oral phosphate supplementation alone (Tieder, Arie and Bab, et al., 1992; Econs, et al. 1994).

Table 2.1 Inherited types of primary hypophosphatemic rickets (excluding XLH)

Disorders	Type of inheritance	Clinical features
Hypophosphatemic bone disease	autosomal dominant	Renal phosphate wasting with minimal skeletal changes.
Hereditary hypophosphatemic rickets with hypercalcuria (HHRH)	autosomal recessive	Renal tubular phosphate handling is impaired. The diagnostic features include elevated circulating 1,25-(OH) ₂ D ₃ levels, increased intestinal calcium absorption, hypercalciuria, and osteopenic bone.

There is one more well characterised condition associated with renal tubulopathies resulting in a phosphate leak with consequent bone disease. It is acquired via a tumour, oncogenic osteomalacia. The condition is associated with rare, usually mesenchymal tumours. It is characterised by hypophosphatemia, phosphaturia, and low concentrations of 1,25-(OH)₂D₃ (Rowe, 1994). Nelson and his colleagues (1997) proposed the unifying hypothesis of oncogenic osteomalacia and XLH, but that did not explain all the available data. However, it is possible that hormone(s) with little or no role in XLH may be responsible for oncogenic osteomalacia (Nelson, Robinson and Mason, 1997).

2.2.5 TREATMENT

The goals of the treatment of XLH include improvement in growth and reduction in the severity of bone deformities and activity limitations. Despite important advances, treatment is not curative, but it is associated with the reduction of complications (Carpenter, 1997).

2.2.5.1 Medical treatment

Before 1970, treatment of XLH consisted of vitamin D₂ (calciferol) in large doses. However, this was frequently associated with features of vitamin D toxicity without marked healing of the bone disease. In 1972, the therapeutic benefit of adding

inorganic phosphate supplementation to vitamin D₂ treatment was demonstrated (Rasmussen et al, 1983). However, the treatment with phosphate alone was found to impair calcium absorption, resulting in hypocalcemia and secondary hyperparathyroidism (Latta, et al., 1993). Since the early 1980s, the relatively poor efficiency and complications of large doses of vitamin D₂ (hypercalcuria, hypercalcemia and nephrocalcinosis) favoured a change to shorter acting potent forms of vitamin D, such as 1,25-(OH)₂D₃ (calcitriol) or 1 α -hydroxyvitamin D₃ (alfacalcidol or 1 α -OHD₃) when administered with phosphate. These bioactivated forms of vitamin D are expected to have fewer adverse effects (Eddy, McAlister and Whyte, 1997).

Phosphate and vitamin D metabolites

At present, combined therapy of phosphate and 1,25-(OH)₂D₃ or 1 α -OHD₃ is the best approach. The effects of combined treatment (R₂) can be seen in the pictures of a white girl with XLH (see Fig 2.3).



FIGURE 2.3 Picture of a white girl with XLH
(Reproduced with permission from Glorieux, F H)

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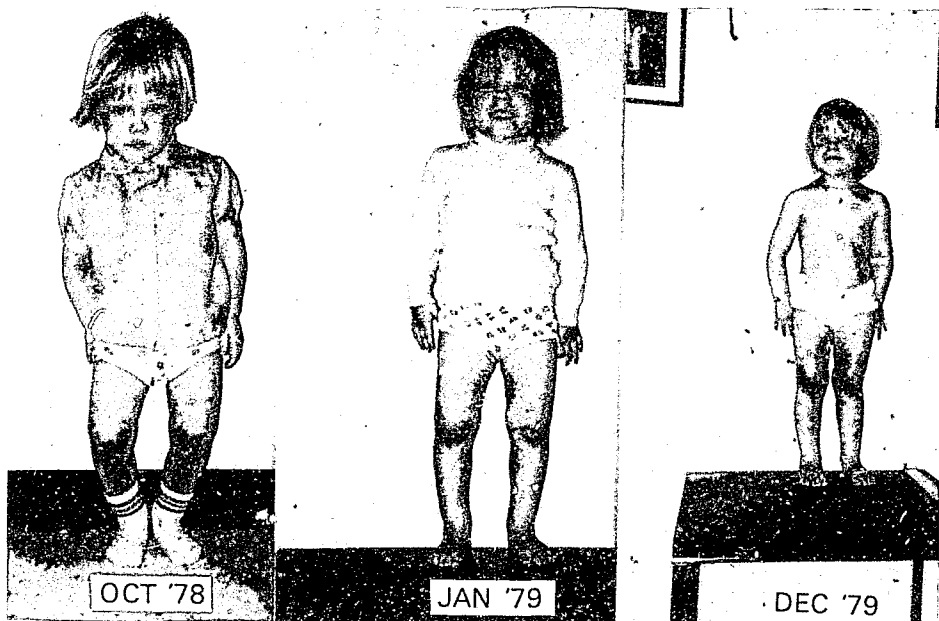


FIGURE 2.3 Picture of a white girl with XLH
(Reproduced with permission from Glorieux, F H.)

The 1st picture was taken in October 1978 before onset of treatment. The 2nd picture was taken in January 1979, after the child was treated with phosphate. The last picture was taken in December 1979, after the child was treated with both phosphate and 1,25-(OH)₂D₃ which shows dramatic improvement of the child. However, conventional treatment of XLH with oral phosphate and 1,25-(OH)₂D₃ or 1 α -OHD₃ does not correct the metabolic or physical defects of the disease, but if the treatment is adequate, growth rates usually increase and the healing process starts. At present treatment is continued until late adolescence, when growth has stopped and the epiphyses have fused (Pettifor, 1998).

Many researchers have investigated the effects of medical treatment on height. Most investigators agree that a positive effect on growth occurs with standard therapy with 1,25-(OH)₂D₃ or 1 α -OHD₃ and phosphate (Rasmussen, Pechet and Anast, et. al., 1981; Balsan and Teider, 1990; Kooh, Binet and Daneman, 1994). A long-term prospective trial of the effects of a standardised regimen on final adult height has not been performed but lessons from available studies are pertinent (Carpenter, 1997). Some studies have demonstrated that growth in girls tends to be better than in boys (Peterson, Boniface and Schranck, 1992; Verge, Cowell and Howard, et al., 1993). Friedman, et al., (1993) described variable responses to treatment in the North Carolina population, with the outcome highly dependent on the height percentile at the onset of therapy. Such findings suggested that the early years of the disease are important in the genesis of the stature deformity. Some argue that the degree of final height impairment is in part related to the severity of disease throughout childhood. Most descriptions of early intervention strongly suggest that medical therapy in the first two years of life results in an improved outcome (Carpenter, 1997).

As with growth effects, bone lesions seem to best respond to treatment with phosphate and 1 α -OHD₃. No long-term prospective trial of the effects of a standardised regimen on the severity of bone disease has been performed but lessons from available studies suggest that fewer osteotomies are performed since 1,25-(OH)₂D₃ or 1 α -OHD₃ has become available (Carpenter, 1997). The effects of treatment (Rx) on bone can be seen in the radiographs of an affected patient on treatment as shown in Fig 2.4. The first X-ray was taken at the time of presentation. The second X-ray was taken 5 months after

treatment with phosphate, which showed incomplete healing and the last X-ray was taken after 5 month treatment with phosphate and 1,25-(OH)₂D₃, which shows better healing than the second X-ray

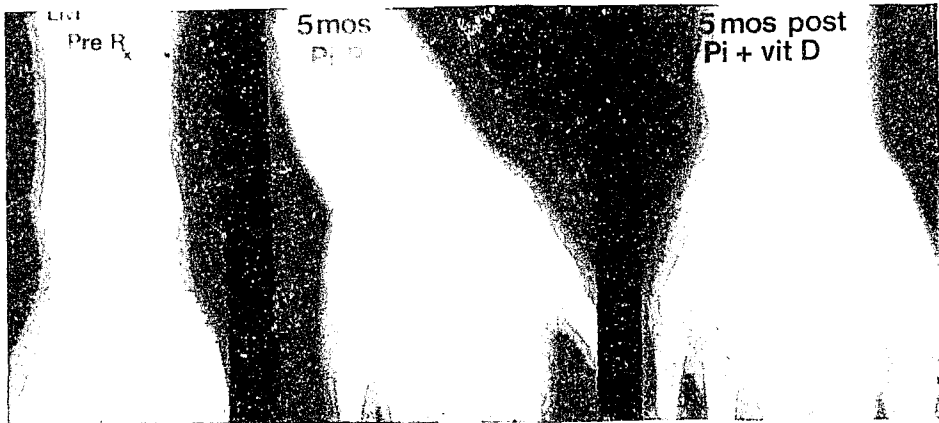


FIGURE 2.4 Radiograph of a patient with XLH on treatment
(Reproduced with permission from Glorieux, F H.)

The dosage ranges of 1,25-(OH)₂D₃ or 1 α -OHD₃ and phosphate in XLH patients are wide, depending on the severity of the rickets, response to therapy and complications encountered. An important principle of therapy is to maintain an appropriate balance in the use of two types of medication. Marked overuse of 1,25-(OH)₂D₃ results in hypercalcemia and hypercalciuria, whereas unopposed phosphate increases may result in secondary hyperparathyroidism (Carpenter, 1997).

Small children should be investigated every 3 months. During stable growth periods, the patients can be seen every 4 to 6 months if there are no complications. Patients should be closely monitored starting just before the anticipated growth spurt. The rapid growth occurring with puberty might result in considerable worsening of bowing defects and a transient increase in medical therapy may be advantageous (Carpenter, 1997). Whether this treatment should be continued in adulthood or during pregnancy is not settled.

Latta, et al., (1993) reviewed the treatment regime of XLH and proposed and phosphate supplementation (70-100mg/kg/day) and 1,25-(OH)₂D₃ (5-50 ng /kg/day). Calcitriol is used in later childhood at a dose averaging 0.75 µg /day and rarely exceeding 1.5 µg/day. If there is hypercalcemia or hypercalcuria with normal PTH values, borderline vitamin D intoxication might be present, indicating the need for a decrease in 1,25-(OH)₂D₃ dose, or if severe, temporary cessation of all therapy. After the end of the growth spurt, and achievement of final height, dosage may be lowered to an adult maintenance dose. Carpenter (1997) suggested an adult dosage of average of 0.75µg/day of 1,25(OH)₂D₃.

Dosage of elemental phosphate should average 1 g/day and rarely exceed 2g/day. Diarrhoea, bloody stools or persistent dose related abdominal pains indicate a need for reassessment of schedule of administration and a probable reduction in total phosphate dose. The development of secondary hyperparathyroidism is an indication to alter the 1,25-(OH)₂D₃/ phosphate balance by decreasing phosphate or increasing the 1,25-(OH)₂D₃ dosage. In the event of a poor clinical response, an increase in the dosage of phosphate with concomitant increase in 1,25-(OH)₂D₃ is recommended (Carpenter, Mitnick and Ellison, et al., 1994).

Other therapeutic measures

Thiazide diuretics or amiloride have been suggested as adjunctive therapy in patients with XLH. The goal of this measure is to increase renal calcium reabsorption and to enhance mineralisation (Alon and Chan, 1985). The long term effects of this measure have not been reported.

New therapeutic approaches such as human growth hormone therapy, may improve linear growth, decrease phosphate loss, and increase 1α-hydroxylase activity (Wilson, Lee and Moris, 1991; Saggese, Baroncelli and Bartelioni, 1995; Patel, Clayton and Brain, et al., 1996; Seikaly, Brown and Baum, 1997). In another study, the children with XLH were found to benefit from the positive effects of recombinant human growth hormone on growth and BMD (bone mineral density) (Reusz, Miltenyi and Stubnya, et al., 1997). However, there are concerns about the use of growth hormone

in patients with XLH, because it may not only cause increased growth rate but also increased deformities. Further, the expense of such therapy might preclude it from use on a long term basis (Carpenter, 1997).

Non hypercalcemic vitamin D analogues like 24, 25 dihydroxyvitamin D₃ supplementation have been considered as adjunctive therapy in patients with XLH to maximise skeletal effects and suppress the development of hyperparathyroidism (Carpenter, Keller and Schwartz, et al., 1996; Ono and Seino, 1997).

Complications of medical treatment

Three major complications of therapy for XLH are: hypervitaminosis D, hyperparathyroidism and soft tissue calcification (Carpenter, 1997).

Hypervitaminosis D is manifested by hypercalcemia and hypercalciuria. Its occurrence is more frequent with high doses of fat-soluble vitamin D and infrequent monitoring of serum and urinary biochemistry (Carpenter, 1997).

Hyperparathyroidism is not an uncommon occurrence in XLH. The stimulatory effect of phosphate treatment on PTH secretion has been well described in patients. Therefore, phosphate supplementation should never be given alone. Concomitant use of vitamin D dampens this PTH stimulatory effect of phosphate and should be part of the treatment regime. Elevated PTH levels are more likely to be detected at night. Isolated cases of tertiary hyperparathyroidism have been reported. It is unclear whether this is a primary result of XLH or secondary to therapy (Carpenter, 1997).

Soft tissue calcification particularly at the level of renal medullary pyramids (nephrocalcinosis) detected by ultrasound is a recognised abnormality for some patients with XLH who receive vitamin D₂ or 1,25-(OH)₂D₃ and inorganic phosphate therapy (Reusz 1995; Taylor, Sherman and Norman, 1995; Alon, 1997). Eddy, et al., (1997) found that subradiaphragmic medullary nephrocalcinosis acquired during medical therapy for XLH may persist for decades but with no adverse renal sequelae. They suggested that definitive long term assessment of kidney function should be carried out in the XLH patients with nephrocalcinosis.

2.2.5.2 Surgery

Despite the advantages of medical therapy, some patients require surgical correction of severe limb deformity. The approach to surgery for XLH patients is physician dependent. However, if the bowing is so severe that irreversible progression of the varus deformity is unavoidable with continued growth even with medical therapy, then surgery is recommended. Some clinicians suggest that children younger than 6 years of age should not undergo corrective orthopaedic surgeries because bow defects at this age are usually not severe and aggressive medical therapy may correct the deformity over time (Kanel and Price, 1995). Surgical procedures may vary. Fixations with plating and stapling, and more recently external fixation devices, have been used. One report emphasised that in adults, fixation by intermedullary nail or rod placement achieved optimal results (Eyres, Brown and Douglas, 1993). Medication dosage might require adjustment because of immobilisation-associated hypercalcemia following osteotomy. However, an optimal medication schedule should be maintained to facilitate healing of the osteotomy. Recently, leg-lengthening procedures have been attempted in a few patients with XLH (Verge, et al., 1993).

2.2.6 SUMMARY

XLH is the most common heritable form of rickets. Affected individuals frequently present with the following characteristics: short stature, lower extremity deformity, bone pain, dental abscesses, rickets and osteomalacia. Females with XLH appear to be less severely affected than males, probably due to the lyonization of one of the X chromosomes. XLH is biochemically characterised by hypophosphatemia, normocalcemia, normal plasma PTH, and inappropriately low $1,25-(\text{OH})_2\text{D}_3$ and renal phosphate wasting. Radiologically, it is characterised by evidence of rickets without features of osteopenia. Treatment is aimed at correction of hypophosphatemia and improvement in growth, and reduction in severity of bone deformities which could result in activity limitations. At present, combined therapy of phosphate and $1,25-(\text{OH})_2\text{D}_3$ or $1\alpha\text{-OHD}_3$ is the best approach. Despite the advantages of medical therapy, corrective orthopaedic surgery is required for patients with severe limb deformities.

2.3 GENETICS OF XLH

XLH is inherited as an X-linked dominant trait with the mutant gene being located on the distal part of the short arm of the X chromosome. Thus both males and females can be affected. However, in males the condition is uniformly severe, whereas in the female heterozygotes are more variably affected due to Lyonization (Muller and Young, 1995).

2.3.1 X-LINKED DISORDERS

Although the X chromosome is involved in sex determination, most genes on the X chromosome have functions unrelated to sex. For an X-linked locus with two alleles (A or a), females can be of one of the three genotypes, AA, Aa or aa. Since males have a heteromorphic XY sex chromosome pair, they are hemizygous (carry only one allele) for each X-linked locus; thus only two genotypes are possible in males, A or a. For an X-linked locus, the genotype of each son is determined solely by the mother, whereas both parents contribute to the genotype of each daughter. X-linked inheritance can be either recessive or dominant. The phenotypic distribution of an X-linked trait in a family depends on whether the trait is dominant or recessive. If a single dose of a gene is sufficient to produce a phenotypic effect in heterozygous females, the trait is dominant; if homozygosity is required the trait is recessive (Rivas, 1979).

2.3.1.1 X-linked dominant disorders

Besides XLH, the Xg blood group is also inherited as an X-linked dominant trait. Examples of other rare X-linked dominant disorders are Incontinentia pigmenti, and Orofaciodigital syndrome (Kingston, 1994; Muller, et al., 1995).

An X-linked dominant gene will give rise to a disorder in both hemizygous males and heterozygous females. The gene is transmitted in families (Table 2.2). The following features are necessary to establish X-linked dominant inheritance (Harper, 1995):

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1. Both males and females are affected
2. Females are less severely affected than males
3. Male to male transmission never occurs (because a man does not transmit his X chromosome to his son)
4. All daughters of an affected male will receive the gene, i.e. they will all be affected
5. Unaffected males never transmit the disease to their descendants of either sex
6. The risk to sons of women who are affected is 1 in 2
7. Half the daughters of the affected women will be affected
8. Twice as many females will generally be affected as males

Apparent exceptions to the above may be the result of chromosome disorders, e.g. occurrence of the disease in a 45,X female, or of nonpaternity. In some X-linked dominant disorders, the condition is lethal in hemizygous males (e.g. Incontinentia pigmenti). In this case, there will be fewer males than expected in the family, all of whom will be healthy, and an excess of females, half of whom will be affected.

Table 2.2 Comparison of autosomal dominant with X-linked recessive and dominant inheritance (Connor, et al., 1997).

	X-linked recessive	X-linked dominant	Autosomal dominant with sex limitations
Pedigree pattern	Knight's move	Vertical	Vertical
Sex ratio	M>>F	2F:1M	M>F
Male to male transmission	Never	Never	50% of sons affected
Male to female transmission	All daughters carriers	All daughters affected	<50% of daughters affected
Female to female transmission	50% of daughters carriers	50% of daughters affected	<50% of daughters affected
Male severity	Uniform	Uniform	Variable
Female severity	Mild	Variable	Variable

2.3.1.2 X-chromosome inactivation

As expected for X-linked dominant disorders, females are more often affected than males. However, a gene dosage effect does not seem to exist for renal phosphate

reabsorption. Preferential X chromosome inactivation (Lyonisation) has been proposed as a possible explanation for this lack of gene dosage effect. Orstavik, et al. (1996) examined the X chromosome inactivation pattern in 12 females belonging to 7 families with XLH using PCR analysis at the androgen receptor locus and did not find any difference in comparison with the patterns in healthy females. They suggested that the X chromosome inactivation pattern in peripheral blood cells did not necessarily reflect the X chromosome inactivation pattern in renal cells. However, the finding of a normal distribution of the X chromosome inactivation pattern in peripheral blood cells indicates that the similarity in the renal handling of phosphate in male and female patients is not related to a ubiquitous preferential X chromosome inactivation (Orstavik, et al., 1996).

2.3.2 PATTERN OF INHERITANCE

In XLH like other X-linked dominantly inherited disease, the pedigree (see Fig 2.5) resembles that of an autosomal dominant trait but the key difference is the lack of male-to-male transmission (Fraser Roberts and Pembrey, 1979).

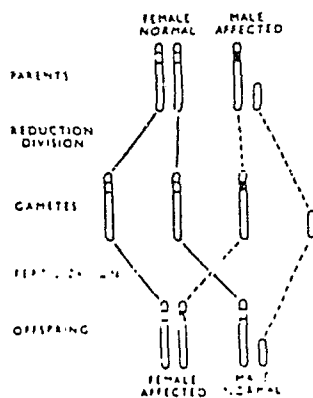


Diagram showing the transmission of the gene in the mating to a normal man of a woman heterozygous for X-linked dominant gene

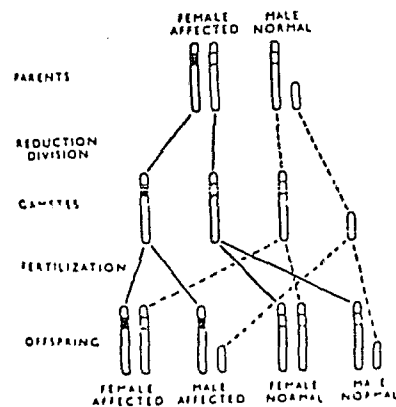


Diagram showing the transmission of the gene in the mating to a normal woman of a man bearing an X-linked dominant gene

FIGURE 2.5 Transmission of X-linked dominant disorder (Fraser Roberts, et al., 1979)

In XLH, the inherited trait may vary in the degree of manifestation from severe to mild bone disease associated with hypophosphatemia alone without evidence of active or former rickets. Rasmussen, et al. (1994) suggested that hypophosphatemia was almost uniformly inherited in this disorder, whereas overt bone disease varied considerably. Therefore, hypophosphatemia provides the best determinant for identifying the trait.

In X-linked conditions, it may be extremely difficult, if not impossible to determine the origin of the disorder when there is only an isolated individual affected; the subject may represent a new mutation or the mother may have inactivation of the affected X chromosome and a functioning normal X chromosome (Carpenter, 1997). The Mendelian risk of having an affected child is 50% in each pregnancy when the pregnant female is affected with XLH, and when the male partner is affected, 100% of the daughters will receive the mutant gene, but none of the sons will (Harper 1995). However, some 30% of cases of XLH appear to be the result of sporadic mutations (Pettifor, 1998).

In most affected children, a sporadic occurrence of XLH is probably caused by a new mutation in the affected gene on the X chromosome and subsequent generations will transmit the disorder in an X-linked dominant fashion (Glorieux, 1996).

Whyte, et al. (1996) studied the potential genetic effects on disease expression in XLH among 116 black and white children in USA and found no evidence for gender, race, anticipation, or parent of origin effects or for genetic heterogeneity. They concluded that the more significant skeletal disease occurring in affected males than in females might be due to differences in sex hormones, physical activity, etc.

2.3.3 MOLECULAR GENETICS

Several recent studies based on genetic linkage and multilocus analysis in humans have allowed fine mapping of the XLH gene to the HYP region (Xp22.1-22.2) of the X chromosome between markers DXS41 and DXS43 (Rowe, Goulding and Read, et al., 1994; The HYP Consortium, 1995). The gene for XLH was called PEX gene (Phosphate regulating gene with homologies to endopeptidases, on the

X chromosome) (The HYP Consortium, 1995). It is now called the PHEX gene (Dixon, et al., 1998). The PHEX gene is composed of multiple exons that span at least five cosmids. Holm, Huang and Kunkel (1997) determined the genomic structure of the PHEX gene, which was found to be composed of 18 short exons. Intragenic non-overlapping deletions and mutations (splice sites and frameshift) have been found in some XLH patients (The HYP Consortium, 1995). Grief, Mumm and Waeltz, et. al. (1997) found that the PHEX gene was mutated in up to 83% of the patients with XLH. Several types of mutations of the PHEX gene found in XLH patients have been described. Dixon, et al. (1998) identified 31 mutations (e.g. nonsense, deletion, insertion, duplication, splice site, missense at the 5' untranslated region). A single stranded conformational polymorphism was found in more than 60% of these mutations. These mutations indicate that the dominant XLH phenotype is unlikely to be explained by haplo-insufficiency or dominant negative effect. Although some mutations may have been missed, the lack of detectable mutations in some patients implies there may be other loci involved in the generation of XLH phenotype (Holm, et al., 1997).

The PHEX gene encodes a protein, which is a member of a large family of endopeptidases with homologies to neural endopeptidases and endothelin-1 activase. They appear to degrade or activate peptide hormones (Carpenter, 1997). The PHEX protein is a 749 amino acid protein consisting of an intracellular, transmembrane and extracellular domain that contains a Zinc binding motif (Dixon, et al. 1998). It has 27-38% identity to other members of metalloendopeptidase family (Guo and Quarles, 1997). Though the function of PHEX is not exactly known, current information suggests that impaired renal phosphate conservation in XLH is due to the failure of PHEX to either degrade an undefined phosphaturic factor, or activate a novel phosphate conserving hormone. It is likely that the PHEX product is involved in the processing of a factor involved in phosphate homeostasis. Mutations would result in abnormal processing of such a factor, thereby disrupting normal phosphate homeostasis. The endopeptidase may act on various substrates accounting for the multiple defects or alternatively the phosphate regulating factor may have various target sites. Furthermore, exposure to hypophosphatemia may have a role in the expression in other defects. Variability in bone disease may be explained by

variability in genetic background or the nature of a particular mutation in a given family (Carpenter, 1997).

Homology of PHEX to the M13 family of Zinc metallopeptidases, which include neprilysin as a prototype, has raised questions regarding PHEX function at the molecular level. The wide range of mutations that align with regions required for protease activity in neprilysin suggests that PHEX also functions as a protease and may act by processing factor(s) involved in the bone mineral metabolism (Rowe, Oudet and Francis, et al., 1997).

The physiologically relevant target tissues for the PHEX mutation have not been identified. An apparent intrinsic defect of osteoblast function in XLH has implicated in bone as a possible site of PHEX gene expression. A study on mice showed that Pex (murine homologue of PHEX gene) mRNA was expressed in bones and teeth and it was suggested that the putative endopeptidase played an important role in the development of these tissues (Ruchon, Marcinkiewicz and Siegfried, et. al., 1998). Beck, Soumonou and Martel, et al., (1997) used reverse transcriptase/ polymerase chain reaction (RT/PCR) and ribonuclease protection assays and found that Pex/PHEX mRNA was expressed in low abundance predominantly in the human fetal and adult mouse calvaria and long bone. A large deletion in the 3' region of the Pex gene was present in the *Hyp* mice (murine model of XLH). On the other hand, Grieff, Whyte and Thakker, et al. (1997) using Northern analysis found abundant PHEX mRNA in a restricted pattern, predominantly in adult ovary, fetal and adult lung, and fetal liver. The presence of PHEX in non-osseous tissues strongly suggested features of a systemic role, rather than a unique function in bone development. Further characterisation of its tissue expression would be needed to dissect out its exact role in phosphate homeostasis and XLH. Once these studies are completed, it would allow comparisons among affected families and between mouse and man (Glorieux, 1996).

2.3.4 MURINE MODELS OF XLH

XLH is a metabolic bone disease occurring in both humans and mice. In mice, two different mutations (*Hyp* and *Cy*), occurring at separate but closely linked loci, have been proposed as models for this disease. The degree of conservatism in the

mammalian X chromosome and comparative mapping of the mouse and human gonosomes, support the contention of a close analogy between the XLH and *Hyp* mutations. Active studies have thus been pursued in parallel in the two species, to better understand the phenotypic expression of the abnormal genes (Carpenter, 1997).

In 1976, a mutant strain in mice, *Hyp*, was reported which manifested rickets and osteomalacia, hypophosphatemia, and a defective renal tubular phosphate reabsorption. These characteristics were transmitted in an X-linked dominant fashion as in XLH. Since then, the *Hyp* mice have become an extremely important tool to investigate the pathophysiology of human XLH (Carpenter, 1997). Grief (1997) using kidney cells from the *Hyp* mice found that the 5' untranslated sequence of the PHEX gene and the mouse equivalent are highly homologous, implying a conserved functional significance. Defective regulation of circulating 1,25-(OH)₂D, similar to that found in XLH, has been demonstrated in *Hyp* mice (Rasmussen, et al., 1994).

Gy (Gyro) is another murine model of XLH. They have many characteristics comparable to *Hyp* mice (Grief, et al., 1997). Although current theory holds that the *Hyp* and Gy represent mutations of two closely linked genes with distinct pathophysiological consequences, Nesbitt and Drezner (1997) reported that the *Hyp* and Gy mice did not represent mutations of two closely linked genes but rather two separate mutations of the same gene. In addition to the metabolic disorders observed in *Hyp* mice, male Gy mice are sterile and show circling behaviour and reduced viability. These two genes might indicate the presence of multiple gene loci in the human disease, with multiple proteins involved in the pathophysiology of the bone disease. (Nesbitt and Drezner, 1997)

2.3.5 SUMMARY

XLH is inherited as an X-linked dominant trait which affects both males and females. However, in males the condition is uniformly severe, whereas in the female heterozygotes are more variably affected due to Lyonisation. The mutant gene for XLH is called PHEX and it is located at the HYP region (Xp22.1-22.2) of the X chromosome between chromosome marker DXS41, and DXS43. The PHEX gene encodes a protein, which is a member of a large family of endopeptidases with

homologies to neural endopeptidases and endothelin-1 activase, and it degrades or activates peptide hormones. The actual function of the PHEX gene is still unknown. Different mutations of the PHEX gene in XLH patients have been described. The phenotype of XLH also occurs in mice and two different mutations (*Hyp* and *Gy*), occurring at separate but closely linked loci, have been proposed as models for this disease in humans.

2.4 PSYCHOSOCIAL ISSUES RELATED TO XLH

2.4.1 INTRODUCTION

As XLH is a dominantly inherited disorder, the psychosocial burden to the patients and their families could be comparable to that seen in other dominant disorders with similar levels of severity. The parents of the affected child may naturally worry about the possible causes and the risk of recurrence, as well as the physical and psychological effects on their child. The task of the genetic counsellor is not only to provide genetic counselling but also to deal with the reactions of the family members to the diagnosis, their anxiety about the future, and their reproductive attitudes and plans (Hollerbach, 1979a). Psychosocial issues related to XLH do not appear to have been studied much in the past. As XLH patients have physical disabilities in childhood (which might be present even in adult life), some of the relevant literature pertaining to physical disability is reviewed here to provide a general overview.

2.4.2 GENETIC COUNSELLING IN XLH

Genetic counselling is a communication process in which information is provided in a non-directive way. Genetic counselling emphasises informed decision-making and provision of medical, psychological, and social support (Arnos, Israel and Cunningham, 1991). Essentially there are three aspects to genetic counselling: the medical aspects (which include diagnosis, prognosis and management), genetic aspects (which include genetic mechanisms and recurrence risks) and psychological aspects (which include understanding and appreciation of the psychological effects) (Emery, 1984). The ad hoc committee on genetic counselling of the American Society of Human Genetics provided a definition of genetic counselling which includes all

issues that should be covered in a counselling session (Fraser, 1974). The definition is as follows:

'Genetic counselling is a communication process which deals with the human problems associated with occurrence, or the risk of occurrence, of a genetic disorder in a family. The process involves an attempt by one or more appropriately trained persons to help the individual or family (1) to comprehend the medical facts, including diagnosis, the probable course of the disorder, and the available management; (2) to appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives; (3) to understand the options for dealing with the risk of recurrence; (4) to choose the course of action which seems appropriate to them in view of their risk and family goals and act in accordance with that decision; (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder'.

It is necessary for genetic counsellors to be aware of the parental reactions to the birth of a handicapped child. The effect on the wish to give birth to further children after a handicapped child has been born should be discussed during genetic counselling. Thereafter, irrational reactions to the birth of a handicapped child may be explored. Feelings of guilt, anxiety, aggression, problems of adolescence and possibilities of psychotherapeutic aid should be discussed (Gerlicher, 1991).

2.4.3 PERCEPTION AND KNOWLEDGE OF XLH

Since XLH is characterised by obvious phenotypic abnormalities, affected persons may be expected to have a high degree of knowledge about the disease. Econs, and his colleagues (1994) used a six page self administered questionnaire with 234 study subjects (mostly adult) at Duke University Medical Centre, Durham, USA. Among the subjects, 57 were affected and the remaining 177 were family members of the affected subjects. The aims of the researchers were to determine whether or not the family members were aware of their disease and if it was properly diagnosed and treated. Although 62% of the affected individuals knew that they had some problems with their bones, only 23% said that they were told by a physician that they had rickets or osteomalacia. This apparent lack of awareness of the diagnosis occurred in spite of the fact that 62% of the affected subjects complained of bone or joint

problems to their personal physicians. Indeed of those patients who had persistent complaints, only 34% were told they had rickets or osteomalacia. Only one patient listed phosphate and vitamin D when asked to list their medication. Despite the presence of XLH in family members, most of the affected individuals had little or no knowledge about the disease. The researchers concluded that the lack of knowledge in affected individuals might be due to limited access to medical care, the patients forgetting that they were told the diagnosis, or the physician's failure to make the diagnosis of the disease. The affected individuals should be made aware of the hereditary nature of their disorder in order to facilitate early diagnosis and treatment of their affected children before they present with severe deformity (Econs, et al., 1994).

2.4.4 PRENATAL DIAGNOSIS

When a pregnancy is at high risk for an X-linked disorder, fetal sexing offers the possibility of determining whether the fetus is a male or a female, thus helping to refine the risk. If the father is affected with XLH, fetal sexing may be requested for a pregnancy with a view to termination of female fetus, which would inevitably be affected (Harper, 1995). Prenatal diagnosis in XLH is questionable since normal intellect and life expectancy accompany the physical abnormalities. The acceptability of termination of pregnancy to a couple must be determined before any prenatal procedures are contemplated. In some cases, it is unacceptable on religious grounds or because of the prevailing attitude of the community; in others, it is a more personal ethical view. However, unacceptability of termination should not be considered as automatically ruling out prenatal diagnosis, since some patients wish to prepare themselves for accepting an affected child (Hollerbach, 1979b).

2.4.5 PSYCHOSOCIAL ASPECTS OF PHYSICAL DISABILITY

XLH is associated with physical deformities, particularly of the lower limbs. Disability may challenge some basic assumptions about the world and some psychological aspects of self may be profoundly violated. The losses incurred in disability, whether minimal or major, physical, psychological, symbolic, or all of these, may lead to some predictable human emotional responses, although individual

patients' and their parents' responses do vary (Langer, 1994). Therefore, when the broader aspects of health are considered especially when assessing the life of the disabled, it becomes necessary to reach beyond physical measurements to more dynamic aspects including the individual's other resources and demands (Lindström and Köhler, 1991). Factors including concurrent life stressors, social and financial resources, intrapsychic functions, psychodynamic issues, and personal/ subcultural issues may influence the experience of disability (Langer, 1994)

In such a context, issues of quality of life are important. Quality of life is here defined as a term describing the total existence of an individual or a group and is operationalised in three life spheres: external conditions, interpersonal conditions and personal psychological conditions (Lindström et al., 1991). The quality of life among individuals with severe physical disabilities has greatly improved during the last two decades, partly as a result of well-planned intervention programmes mainly in developed countries. However, some individuals with physical disabilities do not cope well in their everyday life, no matter how long they have had the disability. It has been suggested that those individuals who adjust well do so regardless of the degree of their physical impairment and that the disability per se does not decrease the disabled individual's quality of life. The individual's capacity to cope with everyday life was of great importance. Therefore, occupation or meaningful occupational activities as well as social integration at different stages of life should be taken into account when planning intervention programmes in the future (Viemerö and Krause, 1998). However, for people facing a future with the challenge of physical disability, the pattern of progression of disability over time may be of significance in the development of psychological distress (Macleod and Macleod, 1998). Thus, it is necessary to evaluate the quality of life of the XLH patients by assessing their external, interpersonal and personal psychological conditions before planning any intervention programme and before trying to improve counselling services for XLH patients.

General psychosocial issues must be considered in facilitating the development of children with chronic disabilities like XLH. A coping model and the developmental stages can be used as a framework to assess the impact of disabling conditions on children and the interventions that encourage psychosocial growth. Health

professionals, like genetic counsellors, may play a key role in health promotion by encouraging effective coping and growth for disabled children and members of their families, and they should incorporate psychosocial interventions into their practice (Carlson, Ricci, and Shade Zeldow, 1990). Stevens, Steele and Jutai, et al., (1996) examined the psychosocial issues related to adolescents aged 11-16 years with physical disabilities in Canada and found that there were a number of critical areas of risk for adolescents with physical disabilities to which health promotion efforts should be directed. These included lower levels of peer integration, heightened adult orientation, and low educational aspirations. Wallander and Varni (1998) reviewed a large number of studies conducted primarily over the past 5-8 years on the psychosocial effects of paediatric chronic physical disorders on children and their families. In some of these studies, both children and their mothers, as groups, were found to be at increased risk for psychosocial adjustment problems compared to peers, but there was considerable individual variation in the outcome.

2.4.6 INTERPERSONAL RELATIONSHIPS

2.4.6.1 Family dynamics

XLH is associated with clinical as well as psychological and psychosocial problems for the affected persons and his or her family. Being a parent of a handicapped child is not a role people choose for themselves (Garguilo, 1985). The role is difficult, demanding, often confusing and demoralising. Furthermore, the birth and subsequent presence of a disabled child in a family may define the parents to themselves and to others as less capable of child bearing (Hollerbach, 1979a).

The family members of persons with physical disabilities are part of a family unit whose balance, functioning and development have been disrupted. Factors relevant to physical disability, family system approaches, and psychodynamic theory are influential in treatment. The extent and type of a patient's disability determines the practical and personal impact for the patient as well as the relationship of the family members to the patients. A parent or sibling will each experience different practical and emotional consequences within the context of his/her age, stage of life, and

culture. All these factors affect the meaning of the disability for each family member personally, interpersonally, and within the family unit (Padrone, 1994).

Although the nature and the 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. Parental adjustment is an important outcome in child disability interventions, as well as an important mediating variable for other child and family outcomes, for social support and counselling interventions (Pal and Chaudhury, 1998). Waddington and Busch Rossnagel (1992) assessed the influences of specific characteristics of a child with disability on a mother's role functioning and psychological well being over 112 days. They found that various aspects of a disabled child's condition indirectly affected the mother's psychological functioning via a direct effect on her role functioning. Intervention efforts could be targeted towards her role functioning and specific child characteristics (i.e. physical limitations and emotional/ behavioural adjustment). Maternal mental health often suffers, and the resulting depression affects her role as mother and marriage partner. It may also contribute to the mother's self-doubt about her parental competence (Fisman and Wolf, 1991). Lambrenos, Weindling, and Calam, et al. (1996) investigated the prevalence of maternal depression in the mothers of 96 children and found that there were equally high levels of depression in all groups of mothers regardless of birth status, prediction of disability, or presence of actual disability, throughout the first year of the children's lives. However, depressed mothers were found to have significantly more psychosocial stress.

While the impact on paternal psychological health is less, the fathers of autistic children are nevertheless highly stressed and appear to be particularly vulnerable to the stress generated by these difficult children. Within this family climate, the risks for emotional and behavioural problems for siblings must be evaluated, along with their intrinsic strengths, to plan preventive interventions for these children. Effective work with these families requires an understanding of the evolution of family system problems and their dynamic and reciprocal interaction over time (Fisman, et al., 1991).

Varni and Setoguchi (1993) investigated maternal and paternal depression, anxiety, and marital discord as predictors of depression, anxiety, and low self-esteem in 54 children with congenital or acquired limb deficiencies. Higher paternal depression and anxiety predicted higher child depression and higher anxiety. Higher marital discord also predicted higher child depression and anxiety and lower self-esteem. They found that good family support had a positive effect on child adaptation, as did social support from classmates, teachers, and friends.

2.4.6.2 Depression of parents

Depression, as a natural concomitant to loss, may present in a clinical form or in bereavement and grief patterns, and warrants full consideration (both diagnostically and therapeutically) (Langer, 1994). Depressive illness places an enormous economic burden on health services, the community and the individual patient. It is a serious medical disorder associated with high levels of social and physical disability (Lane and McDonald, 1994). Dytrych, Tyl and Schüller, et al (1991) studied a group of mothers with disabled children and found that a certain proportion of mothers suffered from reactive depression, which was not diagnosed and therefore not treated.

Any deformed child in a family can cause depression in the parents. In a project aimed at testing certain psychoanalytical formulations of depression, it is a necessity to establish an appropriate system for identifying depression. However, the difficulties inherent in obtaining consistent and adequate diagnoses for the purpose of research and therapy have been pointed out by a number of authors. Beck, and his colleagues (1961) described the development of an instrument designed to quantitatively assess the behavioural manifestations of depression which has been widely used by many investigators. The inventory was able to discriminate effectively among groups of patients with varying degrees of depression. It also was able to reflect changes in the intensity of depression after an interval of time. In view of these attributes of reliability and validity, this instrument can be a useful tool for a research study of depression and as a step in the direction of placing psychiatric diagnosis on a quantitative basis. (Beck, Ward and Mendelson, 1961)

Yim, Moon, and Rah, et al. (1996) investigated the psychological characteristics of mothers of children with disabilities. They found that: mothers of children with disabilities suffered from serious psychological distress at the initial diagnosis of their child's disability; the severity of the child's disability had little influence on the degree of the mother's initial psychological distress; and lastly, this distress did not resolve with eight weeks of rehabilitational interventions. They suggested that effective rehabilitation programs should provide sufficient opportunities for repeated follow-up interviews, which offer not only adequate information on the children's disabilities but also *psychological support for the mothers*.

2.4.6.3 Interactions with others

The nature of interactions with teachers, classmates, playmates and other children may be a potentially modifiable predictor for the psychological and social adaptation of children with visible physical handicaps. Varni and Setoguchi (1991) investigated social support, daily hassles and psychological adjustment in 51 children with congenital or acquired limb deficiencies. They found that social support from classmate, parent, and teacher, daily hassles, peer acceptance, scholastic and athletic competence accounted for 78% of the variance in perceived physical appearance in those children.

2.4.7 PSYCHOLOGICAL EFFECTS ON PATIENTS

Children with chronic physical handicaps have been found to be at risk for psychological and social adjustment problems. 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 (Varni and Setoguchi, 1992). Disabled teenagers may have problems making the transition from adolescence to adulthood. Helping parents, particularly mothers, 'let go' is an important part of the medical management, as is co-ordinating the complex medical, social, and educational aspects. Issues like sexuality, dating, dressing, and driving must be considered during counselling (Thompson, 1990). The social implications of disability may affect the sexual development of adolescents

Yim, Moon, and Rah, et al. (1996) investigated the psychological characteristics of mothers of children with disabilities. They found that: mothers of children with disabilities suffered from serious psychological distress at the initial diagnosis of their child's disability; the severity of the child's disability had little influence on the degree of the mother's initial psychological distress; and lastly, this distress did not resolve with eight weeks of rehabilitational interventions. They suggested that effective rehabilitation programs should provide sufficient opportunities for repeated follow-up interviews, which offer not only adequate information on the children's disabilities but also psychological support for the mothers.

2.4.6.3 Interactions with others

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with physical disabilities (Meeropol, 1991). Role modelling by successful disabled adults and counselling assist in successful transition (Thompson, 1990).

2.4.8 SUMMARY

As XLH is associated with limb abnormalities, the psychosocial burden on the patients and their families could be comparable to those experienced by others with such abnormalities. The task of the genetic counsellor and other health professionals who deals with these families is to understand their reactions to the diagnosis, their anxiety about the future, their psychosocial issues, family dynamics and reproductive attitudes. Genetic counsellors and other health professionals should also recognise the nature of the disruption of life caused by the disease, the depression which can occur in parents trying to cope with it and the other psychosocial issues associated with having a disabled child in the family. With this improved insight, they can provide a better service to the affected families.

2.5 SUMMARY AND CONCLUSION

Acquired forms of rickets are commonly found throughout the world but with the improvement of health, nutrition, and living conditions, the number of inherited cases like XLH in comparison to other form of rickets is on the rise. However, the pathogenesis of XLH is still not clearly understood, although the medical control of its clinical expression has greatly improved over the past 15 years. The discovery of the PHEX gene has helped in understanding the pathophysiology of the disorder although no studies have been undertaken on PHEX gene mutations in South African patients. The combination of phosphate and 1,25-(OH)₂D₃ or 1 α -OHD₃ allows improved bone growth and adequate bone mineralisation, but it has failed to correct the abnormalities completely. XLH presents as a physical and psychosocial burden in families with an affected patient, but little research has been undertaken on the latter aspect of the condition. It is therefore appropriate, to undertake further specific studies on XLH in these areas.

CHAPTER 3

METHODOLOGY AND PROCEDURES

3.1 INTRODUCTION

The methodology for this study was determined by the aims specified for each of the three sections viz. the clinical study, genetic study and psychosocial study. In this chapter, the setting, scope and design of the study, the selection of the subjects and research tools, and the pilot study to assess the appropriateness of these tools, will be covered. Further, the collection of the data will be described and the methods of data analysis and statistical testing will be specified.

After approved by the 'Post Graduate Committee' (see letter of approval in Appendix A) and 'Committee for Research on Human Subjects (Medical)' of the University of Witwatersrand (see clearance certificate Ref. No. M980204 in Appendix A), the study was initiated in two phases, a retrospective phase and a prospective phase, details of which are described below.

3.2 SETTING AND SCOPE OF THE STUDY

The setting of the study was mainly the Gauteng Province. However, affected families, who attended the clinics of MMRU and SAIMR, from other parts of South Africa and from neighbouring countries were also included. The study was based in the MMRU at Chris Hani Baragwanath Hospital but facilities and records of the MMRU clinic at the Johannesburg Hospital and the genetic counselling clinic at the Department of Human Genetics, School of Pathology, SAIMR and University of Witwatersrand were also used. Most of the required biochemical tests were performed at the laboratory attached to the MMRU at the Chris Hani Baragwanath Hospital but some were performed at the SAIMR and other local private laboratories. The X-rays were taken mainly at the radiology departments in Chris Hani Baragwanath Hospital and Johannesburg Hospital but some were done at other private clinics. The bone density scans were done at the DXA (Dual energy X-ray Absorptiometry) unit

attached to MMRU at the Johannesburg Hospital. It was planned that at least 50 patients and their families would participate in the study and that the data would be collected over a 12-month period.

3.3 DESIGN OF THE STUDY

This study consisted of two parts, a retrospective and a prospective part and three sections: a clinical, genetic and psychosocial section.

1. Clinical study

This section of the study consisted of two parts: a retrospective and a prospective part. In the retrospective part of the study, the records of all the XLH patients investigated at the clinics of MMRU and SAIMR were obtained and reviewed. Details on each subject's clinical, biochemical and radiological data were recorded to determine age and clinical picture at presentation, responses to treatment, and to identify the factors influencing that response.

For the prospective part of the study, attempts were made to contact all the patients on the subject list. Those contacted, were asked to participate in the prospective part of the study. Those patients who agreed and came to the MMRU clinic, were examined and a blood sample was collected for biochemical investigations. These clinical examinations were completed at the MMRU clinic at either Chris Hani Baragwanath Hospital or Johannesburg Hospital. A checklist of items (see Appendix B) was compiled for collecting data on the clinical findings on each patient. Blood samples were collected to establish blood levels of calcium (ionised and total), magnesium, phosphate, alkaline phosphatase (total), creatinine, intact PTH, and 25-OHD₃, and 1,25-(OH)₂D₃. Urine samples were collected to calculate TRP, TmP/GFR and calcium/ creatinine ratio.

2. Genetic study

The data for this section of the study were collected from the review of the records and pedigrees contained therein of 50 patients with XLH. Further details were

obtained from the interviews with the parents of 20 affected patients and with 7 older patients (16 years or older) themselves, who came to the clinic during the period of study. From these family pedigrees, attempts were made to determine the rate of hereditary and sporadic forms of XLH in this series of patients and to assess whether there were any ethnic differences associated with the two types. Efforts were also made to determine from the history the effects of sex, ethnicity of the patient, and type of mutation (hereditary or sporadic) on the severity of the disorder.

3. Psychosocial study

The parents of those patients, who came to the clinic, were asked to participate in this section of the study. If they agreed, they were given an information sheet (in which the nature of the project was explained) to read and a consent form to sign and they were then interviewed. The older patients (16 years or older) were also requested to take part and if they acceded, they were given an information sheet (in which the nature of the project was explained) to read and a consent form to sign and they were then interviewed. The information sheets and consent forms appears in Appendix C. A schedule of questions (see Appendix D) was specially constructed for use in face-to-face interviews to obtain information on the psychosocial issues associated with XLH.

The schedule contained questions on the basic biographical details of the family, their perception of XLH (based on their experience with the disease and what they had been told by health care professionals), their problems and needs, and the myths and beliefs surrounding the disorder. Attitudes to reproduction and carrier testing of the parents of the affected child were also investigated. The schedule was initially tested for length and comprehensibility in a pilot study.

A validated questionnaire on depression (Beck depression inventory) was included to assess depression in the parents. The items in that inventory were primarily clinically derived. It consisted of 21 categories of symptoms and attitudes. Each category described a specific behavioural manifestation of depression and consisted of a graded series of self evaluative statements. The statements were ranked to reflect the range of severity of symptoms from neutral to maximum severity. The items were

chosen on the basis of their relationship to the overt behavioural manifestations of depression and did not reflect any theory regarding the aetiology or the underlying psychological processes in depression. Numerical values from 0-3 were assigned to each statement to indicate the degree of severity. The subjects could therefore score between 0 and 63 where 0 indicated no depression and 63 extreme depression. The interpretation of the results is shown in Table 3.1 (Beck, et al., 1961; Beck and Beamesderfer, 1974).

Table 3.1 Interpretation of results of Depression Inventory
(Beck, et al., 1974)

Total score	Levels of depression
0-10	These ups and downs are considered normal
11-16	Mild moody disturbances
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
41-63	Extreme depression

According to Beck and his colleagues (1961), the significant relationship that they found between the scores on the inventory and the clinical ratings of the depth of depression attested to the validity of this instrument.

3.4 SELECTION OF SUBJECTS

The subjects for this study were ascertained from three sources.

1. MMRU clinic at Chris Hani Baragwanath Hospital: The records available for a twenty-three years period (since the clinic was started) were reviewed. The clinic at MMRU has been a referral clinic for patients with rickets living in the northern provinces of South Africa, i.e. Gauteng, Northern Province, North West Province, Mpumalanga and also for those from other neighbouring countries. Since 1975, approximately 500 patients have been seen at this clinic and 35 (7%) of them had XLH.
2. The MMRU clinic at Johannesburg Hospital: The records from the last 20 years (since the clinic was started) were reviewed and the files of 11 patients with the diagnosis of XLH were found.
3. The genetic counselling clinic of the SAIMR: The records of past twenty-five years

were reviewed and the files of four patients with XLH were obtained.

Names, addresses and telephone numbers for these patients were noted and they were contacted, where possible, and requested to participate in the present study.

3.5 CONSTRUCTION OF THE CHECK LIST AND SCHEDULE OF QUESTIONS

A checklist was compiled for collection of the data necessary for the clinical and genetic study and a schedule of questions was constructed to collect information for the psychosocial part of the study.

The first part of the checklist was used for the clinical study and it consisted of items on:

1. Biographical details e.g. age, sex, ethnicity, home language
2. Age of onset and presentation and presenting complaints
3. Findings at the clinical examination at presentation, at six and twelve months after onset of the treatment and at the last visit to the clinic. The improvement of physical deformities was assessed clinically by the examiners.
4. Anthropometric measurements (head circumference, height, weight and body mass index) at the same time intervals as described in 3 above. The z-scores of the height of the subjects were calculated from their measurements of height in comparison with the standard data (Tanner, Whitehouse and Takaishi, 1966). The z-score of the height is calculated by using the following formula (Petrie, 1990):

$$z = \frac{x - \mu}{\sigma}$$

(x is the height of an individual, μ is the mean height of the population of same age and sex, and σ is the standard deviation of height of the population of same age and sex)

The z-scores of the weight and head circumference were calculated using the same formula from the measurement of weight and head circumference respectively in comparison with the standard data (Tanner, 1978; Jones, 1997)

The body mass index (BMI) was calculated from the combined height and weight measurements by using the following formula (Katzenellenbogen, Joubert and Abdul Karim, 1997):

$$\text{BMI} = \frac{\text{Weight in kg}}{(\text{Height in cm})^2}$$

5. Biochemical test results at the same time intervals as described in 3 above. [calcium (ionised and total), magnesium, phosphate, alkaline phosphatase (total), intact PTH, 25-OHD₃, and 1,25-(OH)₂D₃ in the serum and TRP, TmP/GFR and calcium creatinine ratio in urine].
6. Radiological features at the same time intervals as described in 3 above.
7. Other tests like bone density measurements at the same intervals as described in 3 above.
8. Details of hospital admissions: number of admissions and total duration of admissions
9. History of drug use and compliance
10. History of operations.

The second part of the checklist was used for genetic study and it consisted of the items on:

1. Biographical details of patients
2. Family pedigree

The schedule of questions for the psychosocial section of the study was constructed using the questionnaire presented by Econs et al. (1994) in their study on XLH and the experience of the author and supervisors of the project. Also a validated questionnaire on depression (Beck depression inventory) (Beck, et al., 1961; Beck, et al., 1974) was used to assess depression in the parents.

The first part of the schedule consisted of questions for the parents on:

1. Biographical details of the affected child e.g. age, sex, ethnicity, home language and education
2. Age of the parents at the time of birth of the patient
3. Biographical details of the parents e.g. education, occupation, Social

class (see Table 3.2) was assessed according to the British Registrar General's classification (where social class I is the highest and V is the lowest). Social class was assessed on the basis of the parents' employment (OPCS, 1986) and classified according to the higher of the two parents' occupation.

4. Presenting health complaints of the patients (according to the parents)
5. Parents' perception and knowledge of XLH
6. Reproductive attitudes of the parents
7. Psychological aspects of physical disability e.g. disruption of family life
8. Interpersonal relationships, the effects of the disease on family dynamics and
9. Depression in the parents.

The second part consisted of questions for patients (16 years of age or older) on:

1. Psychological effects of the disease
2. Perception of and knowledge about XLH

The checklist and the schedule of questions appear in Appendix B and D respectively.

Table 3.2 British Registrar General's social class classification (OPCS, 1986)

Social Class		Examples of Occupation
I	Professional	Doctor, lawyer, pharmacist
II	Intermediate	School teacher, manager, nurse
IIINM	Skilled non-manual	Secretary, shop assistant
IIIM	Skilled manual	Carpenter, electrician, cook
IV	Partly skilled	Postman, bus conductor, mechanic
V	Unskilled	Cleaner, labourer

3.6 PILOT STUDY

The schedule of questions was assessed in a pilot study. The pilot study was conducted to detect any unforeseen problems in the use of the schedule, to test the instrument for ambiguous or misleading questions and to assess the length and the time it took to complete.

The schedule was used in interviews with 10 parents whose children were attending the clinic at MMRU in Chris Hani Baragwanath Hospital. The subjects included three

children with a hereditary form of rickets other than XLH and seven with an acquired form of rickets (since so few XLH patients were available for the study, it was decided not to use them for the pilot study). One of the children with an acquired form of rickets had two siblings who had the same condition. The parents were asked to comment on whether the questions were suitable and easily understood and on the length of the questionnaire.

The time taken for completion of the questionnaire was between 30 and 40 minutes and some of the pilot study subjects had problems in answering specific items. The questionnaire was therefore revised by changing the wording of these questions and adding further items. For example, provision was made for 'not known' in Item 11(b).

11 (b) Your child may get this disorder from either you or your partner. Who do you think passed this disorder to your child? You/ Your partner/ Not Known
Does your partner agree with your opinion? Yes/ No/ Not Known

Three new questions, regarding genetic counselling, contacts with other parents and interests in a XLH support group were added. The complete schedule of questions appears in the Appendix D.

3.7 COLLECTION AND ANALYSIS OF DATA

The data for the clinical study were collected from the records of the XLH patients and from the clinical and biochemical examination of those who attended the clinics and were recorded on to the checklist. The data for the genetic study were obtained from the family history and the pedigree and were also recorded on to the checklist. For the psychosocial study, the required information was collected by completing the schedule with the subjects (parents and the patients aged 16 years or older). Where necessary, a translator was used, so that subjects could be interviewed in their home language.

The completed checklists for the clinical and genetic study and the completed schedules of questions for the psychosocial study were coded so that the subjects' names were not written on the sheets or schedules. The data were then computerised and analysed using Microsoft Access software. Statistical analysis of the responses to

the schedule of questions, and the data collected from the records were performed where necessary and statistically significant findings were compared with the findings of other studies.

3.8 STATISTICAL TESTS

The statistical tests used in this study were 1 sample z-test, 1 sample t-test, paired t-test, unpaired t-test, chi-squared test, and Mann-Whitney test. The indications for these tests are described in Table 3.3. The differences were considered to be statistically significant if $p < 0.05$ (Petrie, 1990).

TABLE 3.3 Indications for statistical tests

Indications	1 sample	2 samples	
		Related	Unrelated
Numerical data			
Known population SD*	1 sample z-test		
Unknown population SD*	1 sample t-test	Paired t-test	Unpaired t-test
Nominal data			Chi-squared (χ^2) test
Ordinal data			Mann-Whitney test

*SD- Standard deviation

3.9 SUMMARY AND CONCLUSIONS

This study consisted of two parts, a retrospective and a prospective part, and three sections: a clinical, genetic and psychosocial section. In the clinical section of the study, the records of all the XLH patients (50) investigated at the clinics of MMRU (at Chris Hani Baragwanath Hospital and Johannesburg Hospital) and the genetic counselling clinic of the SAIMR were reviewed. From this review, a list of the names, addresses, and telephone numbers of all the possible subjects with XLH was obtained. For the prospective part of the study, patients and their parents were contacted and asked to participate in the study. A checklist was compiled for use in the record review and clinical examination of the affected subjects. The patients with XLH (26) who attended a clinic were examined clinically, and a blood sample was collected for various biochemical studies. The data for the genetic section of the study were collected from the pedigrees, which appeared in the records of each patient with XLH,

and from their family history. Further details were obtained from the interviews with the parents of 20 affected patients and with 7 older patients (16 years or older) themselves, who came to the clinic during the period of study. For the psychosocial section of the study, a schedule of questions was constructed for use in interviews with parents of the affected children and with patients aged 16 or more years. The data collected in this way were computerised and analysed and submitted to statistical testing where necessary, to produce the findings.

CHAPTER 4

RESULTS

4.1 INTRODUCTION

The information obtained from the completed checklists and schedules of questions was computerised and analysed using the computer program Microsoft Access. Statistical tests were used to assess the significance of the findings. The results obtained from this analysis of the data are recorded in this chapter. The composition of the study groups will be described in detail. Thereafter, the findings of the clinical, genetic, and psychosocial sections of the study will be reported.

4.2 COMPOSITION OF THE STUDY GROUPS

The subjects of the retrospective study consisted of 50 patients from 40 families who were investigated at the clinics of MMRU and SAIMR. They were seen over a period of more than 20 years (from 12/09/1976 until 30/04/1999) and their records were obtained and reviewed. The geographical distribution of their residences is shown in Table 4.1.

TABLE 4.1 Geographical origin of the subjects (N=50)

Place of origin	Number of patients and (%)
SOUTH AFRICA:	
Gauteng Province	35 (70%)
Northern Province	6 (12%)
Kwazulu-Natal Province	3 (6%)
Free State Province	2 (4%)
North West Province	1 (2%)
OTHER COUNTRIES:	
BOTSWANA	1 (2%)
LESOTHO	1 (2%)
SWAZILAND	1 (2%)
TOTAL	50 (100%)

For the prospective part of the study, these 50 patients and their parents were contacted and asked to participate. Those patients (26) who agreed and came to the MMRU clinic were examined. The parents of 20 patients (15 mothers and 5 fathers) were available and were interviewed. Of these 26 patients, only 7 were older than 16 years and could be interviewed personally.

4.3 CLINICAL STUDY

4.3.1 INTRODUCTION

The data for this section of the study were collected from a review of the records of the 50 subjects as well as from the clinical examination of 26 subjects who came to the clinic during the period of study. The aims were to determine the clinical presentation, biochemical and radiological parameters, response to and complications associated with treatment of the affected individuals.

4.3.2 GEOGRAPHICAL DATA

4.3.2.1 Introduction

The first part of the checklist was concerned with the personal details of the subjects. The aim was to obtain information on their age, age of onset of XLH and at

presentation, sex, and ethnic group.

4.3.2.2 Age of onset and presentation

Most of the affected patients had shown symptoms in young 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 to 10 years. Although many presented for treatment several years after the onset of symptoms, five parents (who had XLH themselves) brought their newborn children for diagnosis. The mean age of presentation for diagnosis was 4.65 years with a range of 0.01 to 16 years (see Fig. 4.1). 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.

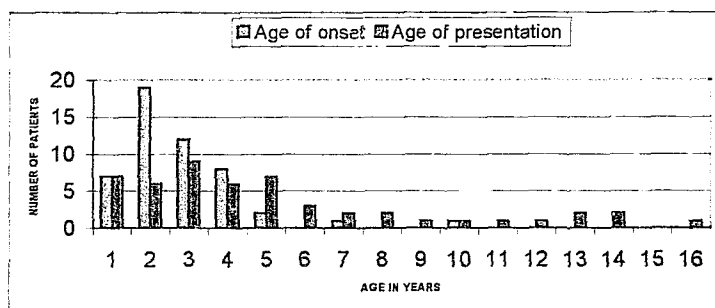


FIGURE 4.1 Age of onset and presentation of XLH (n=50)

4.3.2.3 Sex

There were more affected females (33 or 66%) than males (17 or 34%) and the sex ratio was nearly 2:1.

4.3.2.4 Ethnicity

The ethnic groups of the subjects were as follows: black (31 or 62%), white (17 or 34%) and Asian (2 or 4%). The black patients represented several different language groups as shown in Table 4.2. The white patients spoke either Afrikaans or English (see Table 4.2).

TABLE 4.2 Language spoken by the parents of the subjects (N=50)

Language groups	Father	Mother
Asian (n=2)		
English	2	2
Black (n= 31)		
Zulu	11	10
Shangaan	6	5
Setswana	6	4
Venda	3	5
Sotho	2	3
Swazi	1	2
Sepedi	1	2
Xhosa	1	0
White (n=17)		
English	12	12
Afrikaans	5	5

4.3.3 CLINICAL PRESENTATION

This part of the checklist was concerned with the presenting complaints and other complaints of the subjects. The findings are shown in Table 4.3.

TABLE 4.3 Complaints reported by parents (N=50)

	Number of patients and (%)
MAIN COMPLAINTS	
Bowing of legs	44 (88%)
Problem in walking	8 (16%)
Short stature	5 (10%)
Hereditary (previously affected parent)	5 (10%)
Pain in legs	4 (8%)
Dental problems	4 (8%)
Fractures	3 (6%)
Deformities of hands	2 (4%)
Abnormality in skull	2 (4%)
Hearing problems	2 (4%)
Tiredness	1 (2%)
OTHER COMPLAINTS	
Respiratory	6 (12%)
Renal	1 (2%)
Hepatic	1 (2%)
Mental retardation	1 (2%)

The findings showed that the main presenting complaints were bowing of the legs (88%), problems in walking (16%) and short stature (10%). These problems alerted the parents to seek medical attention. Some parents (10%) brought their newborn children to the clinic because they were XLH patients themselves and they were anxious about whether or not their children were affected.

4.3.4 CLINICAL EXAMINATION

4.3.4.1 Introduction

In this section, the findings regarding the clinical examination of XLH in each subject are described. Their anthropometric measurements and physical deformities were recorded at first presentation and then at every subsequent three monthly visits.

4.3.4.2 Anthropometric measurements

The anthropometric measurements included head circumference, height, weight and body mass index (BMI). Each of these was measured at every clinic visit. The measurements at presentation and 1 year after treatment appear in Table 4.4.

Table 4.4 Anthropometric measurements before and during treatment in subjects with XLH

	At presentation	After 12 months treatment	p value
Head circumference (z-score)			
Number	15	6	
Mean z-score $\pm$ SD*	0.026 $\pm$ 1.47	1.05 $\pm$ 0.73	0.08
Range	-2.54 to 1.63	0.13 to 2	
95% CI**	-0.79 to 0.84	0.27 to 1.82	
Height (z-score)			
Number	35	33	
Mean z-score $\pm$ SD*	-3.47 $\pm$ 1.47	-2.98 $\pm$ 1.65	0.07
Range	-6.39 to -0.15	-6.57 to 2.5	
95% CI**	-3.98 to -2.96	-3.58 to -2.39	
Weight (z-score)			
Number	35	33	
Mean z-score $\pm$ SD*	-1.51 $\pm$ 1.2	-1.11 $\pm$ 1.35	0.06
Range	-4.23 to 1.58	-2.91 to 3.43	
95% CI**	-1.93 to -1.10	-1.59 to -0.64	
BMI			
Number	35	33	
Mean $\pm$ SD*	17.75 $\pm$ 2.8	18.38 $\pm$ 3.32	0.04
Range	10.75 to 24.5	13.78 to 30.95	
95% CI**	16.77 to 18.72	17.2 to 19.56	

*SD Standard deviation **CI Confidence Interval

Statistical analysis using a one sample t-test showed that the z-scores for head circumference at presentation were not significantly different from zero ($p=0.95$). The paired t-test showed that the z-scores of head circumference of the subjects did not change significantly after 1 year of treatment ($p=0.08$).

Statistical analysis using a one-sample t-test showed that the z-scores for height of the subjects at presentation were significantly lower than zero ($p<0.0001$). This indicates that the average height of the subjects at presentation was significantly lower than normal. The paired t-test showed that the z-scores of the height of the subjects tended to increase between the time of first presentation and 1 year after treatment was started ($p=0.07$), although it still remained significantly lower than zero ($p<0.001$). This can be clearly seen in Fig 4.2 and 4.3. The heights of the subjects were plotted on the physical growth charts for boys (Fig 4.2) and girls (Fig 4.3) (National Center for Health Statistics, 1977). These two charts show that the heights of the subjects

remained low in spite of medical treatment and there was generally tracking with no movement through the centile lines.

Statistical analysis using a one-sample t-test showed that the z-scores for weight of the subjects at presentation were significantly lower than zero ($p < 0.0001$). This indicates that the average weight of the subjects at presentation was significantly lower than normal. The paired t-test showed that the z-scores of the weight of the subjects tended to increase between the time of first presentation and 1 year after treatment was started ($p = 0.06$) although it still remained significantly lower than zero ($p < 0.001$).

Statistical analysis using paired t-test showed that BMI was increased after 12 months of treatment, ($p = 0.04$). However, this increase might be due to the normal increase in BMI that occurs in growing children.

4.3.4.3 Physical deformities

Physical deformities were recorded at the time of presentation and at the subsequent visits and the improvement was assessed clinically by the examiners. The data at the time of presentation and at the subjects' last clinic visit were used to evaluate treatment. During this period, they had had medical treatment and, in some subjects, surgical corrections for deformities. Most of the patients improved with treatment and very few did not improve (see Table 4.5).

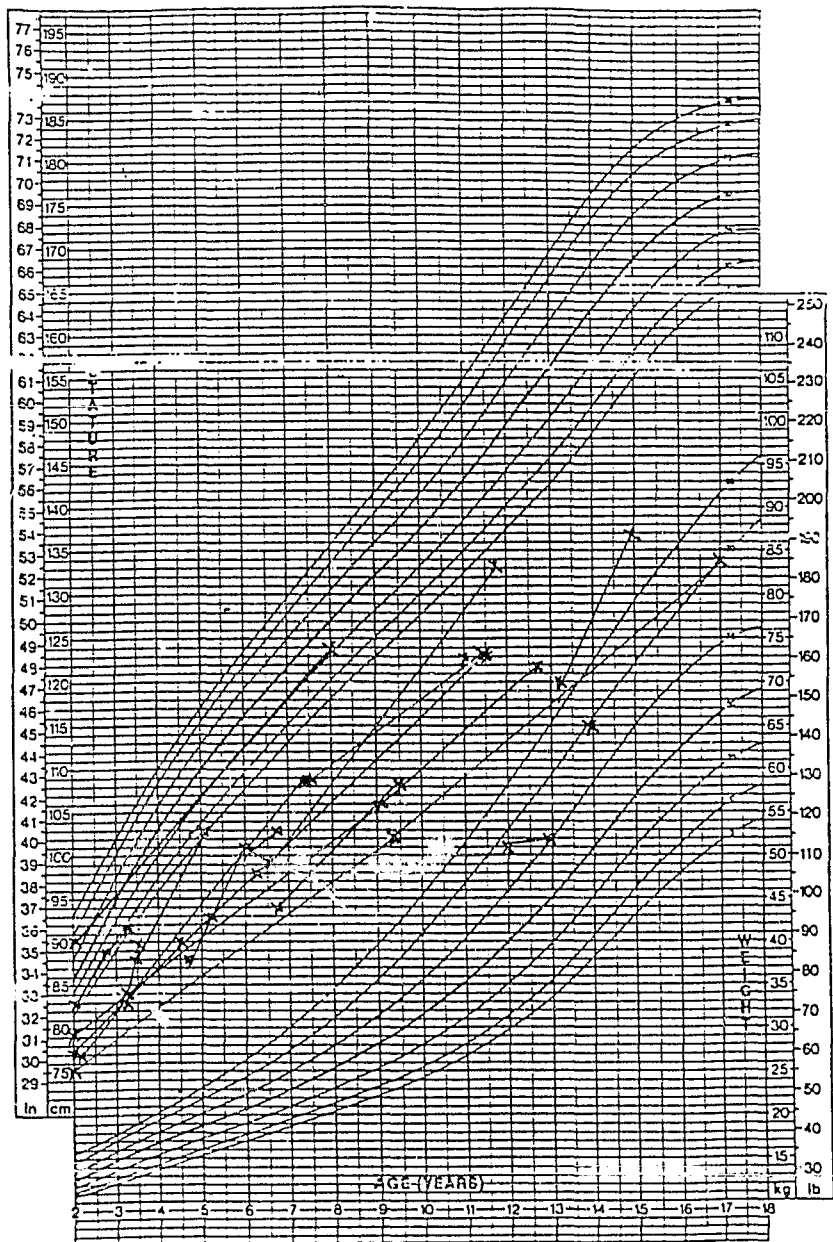


FIGURE 4.2 Physical growth chart for boys aged 2 to 18 years
(National Center for Health Statistics, 1977)

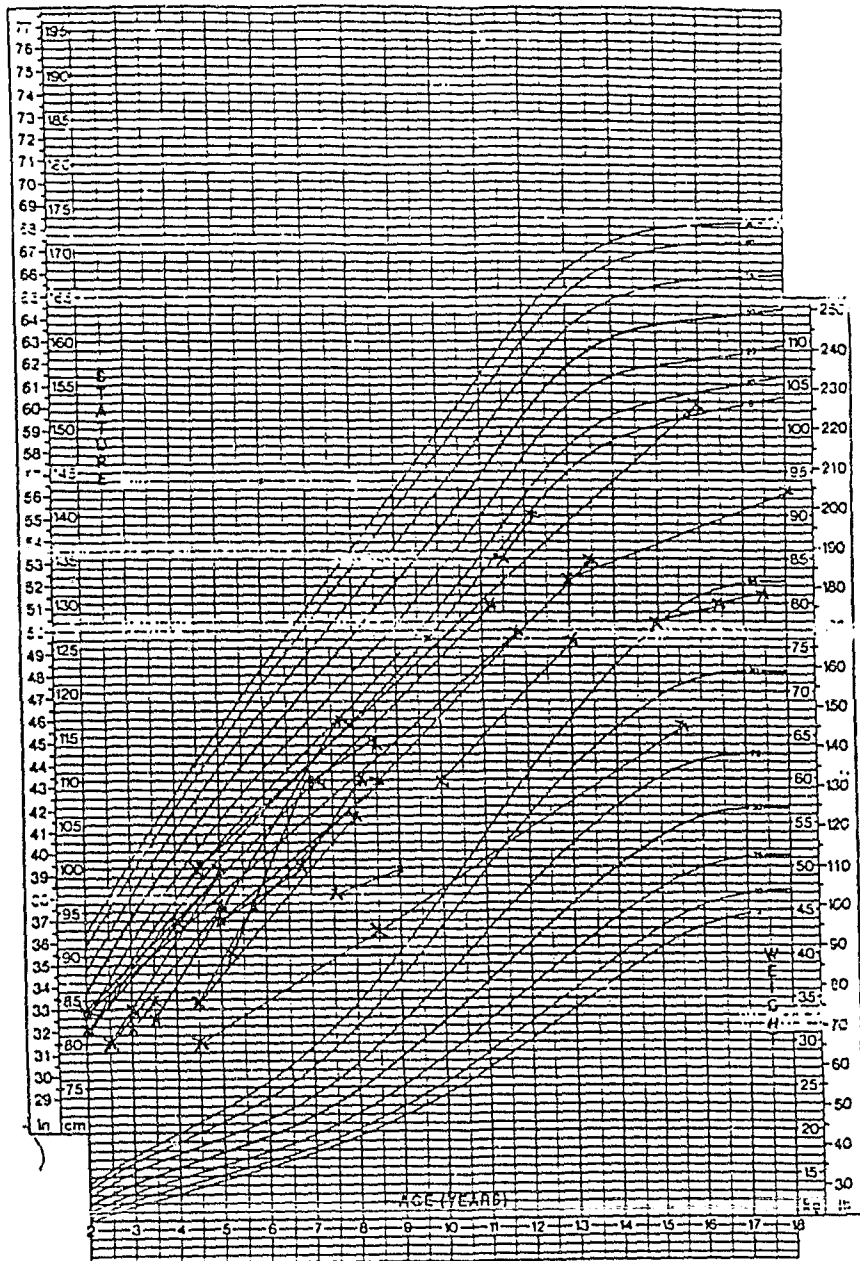


FIGURE 4.3 Physical growth chart for girls aged 2 to 18 years
(National Center for Health Statistics, 1977)

TABLE 4.5 Physical deformities before and during treatment in subjects with XLH (N= 50)

PHYSICAL DEFORMITIES	Number of patients before treatment		Number of patients whose deformity had improved or disappeared during treatment
	Number	(%) of total patients	Number/ total
LOWER EXTREMITIES			
Varus deformities	40	80	38/ 40 (95 %)
Valgus deformities	7	14	6/ 7 (86%)
Joint abnormalities	4	8	3/ 4 (75%)
Fracture of femur	2	4	2/ 2 100%)
Pelvic deformities	1	2	1/ 1 (100%)
Ligamental laxity	1	2	1/ 1 (100%)
UPPER EXTREMITIES			
Widened wrist (splaying)	10	20	10/10 (100%)
Varus deformity of elbow	1	2	0/1 (0%)
SKULL			
Abnormal shape (e.g. scaphocephaly, brachycephaly)	8	16	4/8 (50%)
Frontal bossing	4	8	2/4 (50%)
SPINAL DEFORMITIES	1	2	0/1 (0%)
CHEST			
Rickety rosary	10	20	9/10 (90%)
Harrison's sulcus	4	8	4/4 (100%)

4.3.4.4 Summary

The anthropometric measurements showed that the mean height and weight of the subjects were lower than normal and although they tended to get better with treatment but never reached normal levels. The findings of the clinical examination showed that the main deformities at the time of presentation were deformities of the lower extremities, which improved significantly with treatment.

4.3.5 BIOCHEMISTRY

4.3.5.1 Introduction

The blood and urine biochemistry was routinely done at presentation and then every 6 and/or 12 months for all the XLH patients. The following tests were completed:

Serum calcium (Ca) (ionised and total), serum magnesium (Mg), serum phosphorus, serum alkaline phosphatase (total), serum intact parathyroid hormone (PTH), vitamin D metabolites [25-OHD₃ and 1,25-(OH)₂D₃] and TRP, TmP/GFR and calcium creatinine ratio (Ca/Cr) in urine. However, ionised calcium, magnesium, intact PTH, and vitamin D metabolites [25-OHD₃ and 1,25-(OH)₂D₃] were not measured routinely in all subjects. Intact PTH assays in the laboratory only became routinely available in the mid 1980s, and vitamin D metabolites were only measured, if there were concern that the patient might have vitamin D deficiency. In this section the blood and urine biochemistry results which were collected at presentation (before onset of treatment), 6 and 12 months after the beginning of treatment and at the last visit to the clinic are presented.

4.3.5.2 Serum calcium, magnesium and phosphorus

The details of the serum calcium, magnesium, and phosphorus concentrations before and during treatment are presented in Table 4.6.

TABLE 4.6 Serum calcium, magnesium and phosphorus concentrations in XLH subjects before and during treatment

	BEFORE TREATMENT	DURING TREATMENT		
	At presentation	After 6 months treatment	After 12 months treatment	Last visit
Ionised calcium (mmol/l)				
Number of subjects	9	5	2	8
Mean $\pm$ SD	1.2 $\pm$ 0.04	1.23 $\pm$ 0.07	1.26 $\pm$ 0.01	1.19 $\pm$ 0.08
95% CI	1.18 to 1.23	1.14 to 1.31	1.20 to 1.33	1.23 to 1.26
Total calcium (mmol/l)				
Number of subjects	40	41	38	45
Mean $\pm$ SD	2.36 $\pm$ 0.14	2.38 $\pm$ 0.14	2.36 $\pm$ 0.12	2.38 $\pm$ 0.15
95% CI	2.31 to 2.40	2.34 to 2.43	2.32 to 2.40	2.34 to 2.43
Serum Magnesium (mmol/l)				
Number of subjects	29	28	27	27
Mean $\pm$ SD	0.89 $\pm$ 0.08	0.87 $\pm$ 0.08	0.83 $\pm$ 0.09	0.86 $\pm$ 0.12
95% CI	0.84 to 0.89	0.84 to 0.90	0.81 to 0.88	0.82 to 0.90
Serum Phosphorus (mmol/l)				
Number of subjects	40	42	38	45
Mean $\pm$ SD	0.89 $\pm$ 0.2	1.21 $\pm$ 0.3	1.20 $\pm$ 0.34	1.04 $\pm$ 0.38
95% CI	0.83 to 0.96	1.12 to 1.31	1.09 to 1.31	0.93 to 1.16

Both ionised and total calcium were measured. Serum ionised calcium values are expressed in mmol/l and the reference value for normal individuals is 1.12-1.23 mmol/l (Glorieux, 1996). Statistical analysis using the one sample t-test showed that the ionised calcium values before onset of treatment were not different from the reference values ($p=0.16$). Statistical analysis using the paired t-test showed that there were no significant differences in ionised calcium values when levels at presentation (before onset of treatment) were compared with levels after 6 months and 12 months of treatment and at the last visit.

Serum total calcium values are expressed in mmol/l and the reference value for normal individuals is 2.1-2.55 mmol/l (Glorieux, 1996). Statistical analysis using the one sample t-test showed that the total calcium values before onset of treatment were not different from the reference values ($p=0.07$). Statistical analysis using the paired t-test showed that there were no significant differences in total calcium values when levels at presentation (before onset of treatment) were compared with levels after 6 months and 12 months of treatment and at the last visit.

Serum magnesium values are expressed in mmol/l and the reference value for normal individuals is 0.65-1.05 mmol/l (Glorieux, 1996). Statistical analysis using the one sample t-test showed that the magnesium values before onset of treatment were not different from the reference values ($p=0.23$). Statistical analysis using the paired t-test showed that there were no significant differences in magnesium values when levels at presentation (before onset of treatment) were compared with the levels after 6 months and 12 months of treatment, and at the last visit.

Serum phosphorus values are expressed in mmol/l and the reference value for normal individuals is 1.45- 1.78 mmol/l in children and 0.87-1.45 mmol/l in adults (Glorieux, 1996). Statistical analysis using the one sample t-test showed that the phosphorus values before onset of treatment were significantly lower than its reference values ($p<0.0001$). Statistical analysis using the paired t-test showed that there was a significant increase in serum phosphorus values when levels at presentation (before onset of treatment) were compared with the levels after 6 months of treatment ($p<0.0001$), after 12 months of treatment ($p<0.0001$), and at the last visit ($p<0.01$).

4.3.5.3 Serum alkaline phosphatase (total)

The details of the serum ALP concentrations before and during treatment are presented in Table 4.7.

TABLE 4.7 Serum ALP concentrations in XLH subjects before and during treatment

Serum ALP (U/l)	BEFORE TREATMENT	DURING TREATMENT		
	At presentation	After 6 months treatment	After 12 months treatment	Last visit
Number of subjects	41	40	38	43
Mean $\pm$ SD	822 $\pm$ 397	719 $\pm$ 560	569 $\pm$ 252	468 $\pm$ 247
95% CI	696 to 947	539 to 898	486 to 652	392 to 544

Serum total alkaline phosphatase (ALP) values are expressed in U/l and the reference value for normal individuals is 80-350 U/l (SAIMR, 1997). Statistical analysis using one sample t-test showed that the ALP values before onset of treatment were significantly higher from its reference values ($p<0.0001$). Statistical analysis using the paired t-test showed that there was no significant difference in serum ALP values when levels at presentation (before onset of treatment) were compared with the levels

after 6 months of treatment ($p>0.05$), but there were significant differences in serum ALP values when levels at presentation were compared with the levels after 12 months of treatment ($p<0.001$) and at the last visit ($p<0.0001$), although the values in the majority of patients (79%) had not returned to normal.

4.3.5.4 Serum parathyroid hormone and vitamin D metabolites

The details of the serum intact PTH, 25-OHD₃ and 1,25-(OH)₂D₃ concentrations before treatment are presented in Table 4.8.

TABLE 4.8 Serum intact PTH, 25-OHD₃ and 1,25-(OH)₂D₃ concentrations in XLH subjects before treatment

	BEFORE TREATMENT (at presentation)
Serum intact PTH (ng/l)	
Number of subjects	18
Mean $\pm$ SD	41.34 $\pm$ 23.58
95% CI	29.62 to 53.07
Serum 25-OHD₃ (ng/ml)	
Number of subjects	7
Mean $\pm$ SD	25.35 $\pm$ 11.06
95% CI	15.12 to 35.58
Serum 1,25(OH)₂D₃ (pmol/l)	
Number of subjects	6
Mean $\pm$ SD	80.21 $\pm$ 38.99
95% CI	39.29 to 121.15

Serum intact PTH values are expressed in ng/l and the reference value for normal individuals is 10-70 ng/l (SAIMR, 1997). Statistical analysis using the one sample t-test showed that the intact PTH values before onset of treatment were not different from the reference values ($p=0.82$). The intact PTH was not routinely measured during follow-up.

Measurements of two metabolites of vitamin D, 25-OHD₃ and 1,25-(OH)₂D₃ were done. Serum 25-OHD₃ values are expressed in ng/ml and the reference value for normal individuals is 14-42 ng/ml (Glorieux, 1996). Statistical analysis using the one sample t-test showed that the 25-OHD₃ values before onset of treatment was not different from the reference values ($p=0.16$). The 25-OHD₃ was not routinely

measured during follow-up.

Serum 1,25-(OH)₂D₃ values are expressed in pmol/l and the reference value for normal individual is 60-110 pmol/l (SAIMR, 1997). Statistical analysis using the one sample t-test showed that the 1,25-(OH)₂D₃ values before onset of treatment were not different from the reference values (p=0.77). The 1,25-(OH)₂D₃ was not routinely measured during follow-up.

4.3.5.5 TRP, TmP/GFR and urinary calcium/creatinine ratio

The details of the TRP, TmP/GFR and urinary calcium/creatinine ratio before treatment are presented in Table 4.9.

TABLE 4.9 TRP, TmP/GFR and urinary calcium/creatinine ratio in XLH subjects before treatment

	BEFORE TREATMENT (at presentation)
TRP (%)	
Number of subjects	26
Mean $\pm$ SD	73.21 $\pm$ 19.57
95% CI	65.30 to 81.11
TmP/GFR (mmol/l)	
Number of subjects	26
Mean $\pm$ SD	0.67 $\pm$ 0.23
95% CI	0.58 to 0.77
Urinary calcium/creatinine ratio (mmol/mmol)	
Number of subjects	24
Mean $\pm$ SD	0.19 $\pm$ 0.16
95% CI	0.12 to 0.26

TRP is calculated from the results of phosphorus and creatinine levels in serum and in 2-hour fasting urine specimens (after overnight fasting). TRP values are expressed in (%) and the reference value for normal individual is 85-95% (Glorieux, 1996). Statistical analysis using the one sample t-test showed that the TRP values before onset of treatment was significantly lower than its reference values (p<0.0001).

TmP/GFR is calculated from the results of phosphorus and creatinine levels in serum

and in 2 hours fasting urine specimens (Walton, et al., 1975). TmP/GFR values are expressed in mmol/l and the reference range for normal individual is 1.4-1.8 mmol/l of glomerular filtrate (Rasmussen, et al., 1983). Statistical analysis using the one sample t-test showed that the TmP/GFR values before onset of treatment was significantly lower than its reference values ($p < 0.0001$).

Urinary calcium creatinine ratios (Ca/Cr) are calculated from the results of calcium and creatinine levels in 24-hour urine specimens. Calcium creatinine ratios are expressed as mmol/mmol and the reference value for normal individual is less than 0.6 mmol/mmol. Statistical analysis using the one sample t-test showed that the Ca/Cr values before onset of treatment were not significantly higher than the reference values.

4.3.5.6 Summary

The above findings showed that the serum phosphorus and ALP values and urinary TRP and TmP/GFR values at first presentation (before onset of treatment) were significantly different from the reference values for normal individuals. There were significant changes in the serum phosphorus values when levels before the onset of treatment were compared with the levels at 6 months and 12 months after starting treatment, and at the last visit. A significant improvement was found in total ALP values when the levels before the onset of treatment were compared with the levels after 12 months of treatment, and at the last visit. Other test results (serum Ca, Mg, urinary Ca/Cr ratio) were normal at presentation and no significant differences in these test results were found when levels before onset of treatment were compared with levels obtained during treatment.

4.3.6 RADIOLOGY

4.3.6.1 Introduction

The radiological examination of the lower and upper extremities was undertaken usually at the time of presentation and subsequently as and when necessary. However X-rays for all the patients were not found. After the recent acquisition of a bone

densitometry (DXA) machine (Hologic QDR4500A), bone density was measured in some of the patients (N=9).

4.3.6.2 Radiological examination of lower extremities

The lower extremities (particularly knee joints) are usually examined radiologically at the time of presentation for a diagnosis of rickets. A total of 43 out of 45 patients (whose radiographs were available or commented on) had radiological feature suggestive of rickets. Subsequently the radiological examinations were done to evaluate treatment. It was found that 93% of the patients improved with treatment (see Table 4.10). Two patients had radiological features suggestive of osteomalacia at 30 and 32 years of age respectively.

TABLE 4.10 Radiological findings in subjects with XLH

No	RADIOLOGICAL FINDINGS	Number of patients with abnormality at the time presentation	Number of patients (with abnormalities) who improved after a minimum of 6 months of treatment
		No of patients with abnormalities / Total No of patients	No of patients who showed improvement/ No of patients who had abnormalities
1	Lower extremities	43/45 (95.5%)	40/ 43 (93%)
2.	Upper extremities	16/40 (40%)	14/16 (87.5%)

4.3.6.3 Radiological examination of upper extremities

The upper extremities (particularly wrist joints and hands) are usually examined radiologically at the time of presentation for a diagnosis of rickets. A total of 16 out of 40 patients (whose radiographs were available or commented on) had radiological features suggestive of rickets. When the radiological examinations were done to evaluate the treatment, it was found that 87% of the patients had improved (Table 4.10).

4.3.6.4 Bone mineral density measurements

Bone mineral density (BMD) were measured on nine patients using a Hologic QDR4500A machine to evaluate their bone mass. The z-scores of lumbar spine BMD

are presented in Table 4.11.

TABLE 4.11 Bone mineral density measurements in subjects with XLH (N= 9)

Lumbar spine BMD z-score	At presentation	After minimum 6 months of treatment
Mean $\pm$ SD	-0.47 $\pm$ 1.16	-0.38 $\pm$ 1.05
95% CI	-1.69 to 0.75	-1.0 to 1.62

Statistical analysis using the one sample t-test showed that the z-scores for lumbar spine BMD before the onset of treatment was no different from the reference values ($p=0.36$) which signifies that the patients had normal bone density in the lumbar spine. Statistical analysis using the paired t-test showed that there was no significant difference in z-scores of lumbar spine BMD when levels at presentation (before onset of treatment) were compared with z-scores at least 6 months after treatment had commenced. However, these findings might be influenced by the small sample size and the small time gap between the two measurements in some patients.

4.3.6.5 Summary

The above findings show that 95% and 40% of patients had features of rickets in the lower extremities and upper extremities respectively when they first presented with a diagnosis of XLH for treatment. After they had had at least six months of treatment, most of the patients had improved. This indicates that the radiological examination of lower and upper extremities is a useful tool in the diagnosis of XLH and evaluation of treatment. This study failed to find any abnormality in the BMD measurements of the lumbar spine of the subjects.

4.3.7 TREATMENT

4.3.7.1 Introduction

The type of the treatment available for patients with XLH includes medical treatment with phosphate and vitamin D analogues. Also, surgical correction is sometimes necessary to correct physical deformities, particularly those of the lower limbs, so that walking and physical appearance can be improved.

4.3.7.2 Medical treatment

Initially, the treatment of the XLH subjects in this study consisted of vitamin D₂ (calciferol) in large doses, which was stopped due to side effects of calciferol. After realisation of the true nature (hypophosphatemia) of the condition, a phosphate preparation (Joulie's Solution or Phosphate Sandoz) was used. The vitamin D preparations, 1,25-(OH)₂D₃ (calcitriol) or its analogue (1 α -OHD₃) were added to phosphate preparations to prevent the development of complications. The present medical treatment of XLH consists of phosphate and 1 α -OHD₃. The patients were usually advised to take the above drugs until after completion of puberty. The drug regimen is described in Table 4.12.

TABLE 4.12 Drug regimen for patients with XLH

Drugs	Doses	Number of patients and (%)
Vitamin D analogues:		
Vitamin D ₂ (calciferol)	1000-4000 IU/day	6 (13.3%)
1,25(OH) ₂ D ₃ (Calcitriol)	0.02-0.04 mcg/kg/day	2 (4.4%)
1 α -OHD ₃ (Alfacalcidol)	0.05 mcg/kg/day (under 20 kg) 1.00 mcg/day (over 20 kg)	42 (93.3%)
Phosphate:		
Joulie's Solution (Dibasic sodium phosphate 136g and Phosphoric acid 58.8g/ 1000ml)	20-30 ml/day	10 (22.2%)
Phosphate Sandoz	0.5 -3 g/day in 4 to 5 divided doses	42 (93.3%)

4.3.7.3 Compliance with medical treatment

Compliance with the medical treatment appears to be a major problem in XLH, which is associated with the regular intake of medicine (four to five times a day) for a long duration. In this sample, it was found that 29 (58%) patients had defaulted sometime during their course of treatment.

4.3.7.4 Surgical treatment

Despite the advantages of medical therapy, some patients require surgical correction of severe limb deformities. It was found that of the 50 patients, 35 (70%) subjects had had corrective orthopaedic surgery. Some (4) of them had been operated on more than once. The average age at first operation was 10.16 years (range 3 to 17 years).

4.3.7.5 Hospital admissions

One of the problems associated with this disorder is prolonged hospitalisation of the patients particularly for those from rural areas. It was found that 40 (80%) of the patients had been admitted to hospital. The average number of admissions per patient was 2 and the average duration was 10.35 months (range 1 to 25 months). The main reasons for prolonged admission was the unavailability of drugs in local hospitals, poor compliance, time taken for improvement in biochemical and radiological features and lastly, the surgical procedures.

4.3.7.6 Summary

The above findings showed that the majority of the patients were treated with phosphate supplementation and vitamin D analogue (1α -OHD₃). Poor compliance was a major problem with the medical treatment. In spite of medical treatment, 70% of the patients had corrective orthopaedic surgery. Another problem associated with this disorder was prolonged hospital admissions.

4.3.8 COMPLICATIONS

Three major complications of therapy for XLH are hypervitaminosis D, hyperparathyroidism and soft tissue calcification. However only one patient (2%) had developed features of hyperparathyroidism while on vitamin D (when 1α -OHD₃ was not available). Four patients (8%) developed chronic diarrhoea while taking phosphate. One patient had a foot drop following corrective osteotomy in her leg.

4.3.9 SUMMARY

The data for the clinical part of the study were collected from the review of records of 50 subjects and clinical examination of 26 subjects. The majority of the subjects were female (33 or 66%). There were 31 black subjects (62%), 17 white subjects (34%) and 2 Asian subjects (4%). The mean height and weight of the subjects were significantly lower than normal and although they tended to get better with treatment but never reached normal levels. The findings of the clinical examination showed that the main deformities at the time of presentation were deformities of the lower extremities, which improved significantly with treatment. There were significant changes in serum phosphorus, serum ALP, TRP and TmP/GFR levels, before and after 6-12 months of treatment. There was also significant improvement of radiological features before and after at least 6 months of treatment. The majority of the patients were treated with phosphate supplementation and vitamin D analogue 1α -OHD₃. Poor compliance with medical treatment was a major problem, as 58% of the subjects did not comply fully with treatment. In spite of medical treatment, 70% of the patients had to undergo corrective orthopaedic surgery. Prolonged hospital admissions were also associated with this disorder. Only a few patients had complications like hyperparathyroidism (2%) (when 1α -OHD₃ was not available) and chronic diarrhoea (8%) (while taking phosphate). One patient had a foot drop following corrective tibial osteotomy.

4.4 GENETIC STUDY

4.4.1 INTRODUCTION

The data for this part of the study were collected from the review of the records of 50 patients with XLH. Further details were obtained from the interviews with the parents of 20 affected patients and with 7 older patients (16 years or older) themselves, who came to the clinic during the period of study. A family pedigree was drawn for each subject and it included at least three generations. The aims of the genetic study were to determine the family history and the prevalence of sporadic and hereditary types of XLH, to assess whether there were any ethnic differences in the proportion of hereditary type XLH, the clinical presentation, or age of onset.

4.4.2 FAMILY HISTORY

The 50 patients came from the 41 families. In 27 of the 41 (66%) families, there were no other affected family members. In 14 (34%) families, the hereditary type of XLH occurred and more than one family member(s) was affected. The pattern of relationship, in the families in which XLH was of the hereditary type is described in Table 4.13.

TABLE 4.13 Family history of XLH in 14 families in which XLH was of the hereditary type

Family history	Number of affected
Mother and affected child	
Mother and daughter(s)	12
Mother and son(s)	9
Father and affected child	
Father and daughter(s)	3
Siblings affected	
Sisters	1
Brothers	1
Sister(s) and brother(s)	3
Grandparent and affected children	
Grandparent, children and grand-children	5

4.4.3 PATTERN OF INHERITANCE

4.4.3.1 Type of mutation

From the family history, attempts were made to determine the prevalence of sporadic and hereditary types of XLH. It can be assumed from the family history that 23 (46%) cases were hereditary and remaining 27 (54%) cases were sporadic. Therefore, the sporadic type was slightly more common than the hereditary type in this sample.

4.4.3.2 Sex distribution

Distribution of subjects according to sex and type of mutations is shown in Table 4.14.

TABLE 4.14 Distribution of subjects according to sex and type of mutations

Type of XLH	Male	Female	Male to female ratio	Total
	Number and (%)	Number and (%)		Number and (%)
Hereditary type	7 (14%)	16 (32%)	1:2.3	23 (46%)
Sporadic type	10 (20%)	17 (34%)	1:1.7	27 (54%)
Total	17 (34%)	33 (66%)	1:2	50 (100%)

In the total group of subjects, there were more affected females (66%) than males (34%) which was to be expected in an X-linked dominant disorder like XLH. The male to female ratio was higher in sporadic type than the hereditary type but the difference was not significant ($p=0.77$). The chi-squared test showed there was no significant difference in sex distribution between hereditary and sporadic types ($p=0.77$).

4.4.3.3 Ethnic distribution

Distribution of subjects according to ethnicity and type of mutations is shown in Table 4.15.

TABLE 4.15 Distribution of subjects according to ethnicity and type of mutations

Type of XLH	Black	White	Asian	Total
	Number and (%)	Number and (%)	Number and (%)	Number and (%)
Hereditary type	11 (22%)	10 (20%)	2 (4%)	23 (46%)
Sporadic type	20 (40%)	7 (14%)	0 (0%)	27 (54%)
Ratio of hereditary to sporadic type	1:1.8	1:0.7	2:0	1:1.2
Total	31 (62%)	17 (34%)	2 (4%)	50 (100%)

The chi-squared test was used to compare black and white subjects (Asians were excluded due to the small sample size). No significant difference was found between the distribution of hereditary versus sporadic type in black and white subjects ($p=0.11$), although the sporadic type were more common in black patients (20/31, 64%) than white patients (7/17, 41.2%). This was possibly due to the small sample size or because the proportion of hereditary and sporadic types is same in both population groups.

4.4.3.4 Summary

In the present study, XLH was found to be more common in females than males (the sex ratio was 2:1) as expected in an X-linked dominant disorder. The sporadic type of mutation was slightly but not significantly more common than the hereditary type. However, sporadic type appeared to be more prevalent in the black population, although no statistically significant difference was found between the two groups.

4.4.4 INFLUENCE OF SEX, ETHNICITY OF THE AFFECTED PERSON AND TYPE OF MUTATION ON AGE OF ONSET

4.4.4.1 Introduction

Attempts were made to determine whether the sex and ethnic group of the affected person, or type of mutation (hereditary or sporadic) influenced the age of onset of XLH.

4.4.4.2 Type of mutation

The age of onset of XLH according to type of mutation is shown in Table 4.16.

TABLE 4.16 Age of onset of XLH in years according to type of mutation

Age of onset	Hereditary type of XLH (n= 23)	Sporadic type of XLH (n=27)
Mean (in years) $\pm$ SD	1.54 $\pm$ 0.85	2.41 $\pm$ 1.75
Range (in years)	0.25 to 3.0	1.00 to 9.00
95% CI	1.17 to 1.92	1.7 to 3.1

The age of onset in patients with the hereditary and sporadic type of mutation were compared by using the unpaired t-test. It was found that there was a significant difference between the two groups ($p < 0.05$) and the subjects with the hereditary type of XLH apparently had a significantly earlier age of onset of the symptoms of the disease.

4.4.4.3 Sex distribution

The age of onset of XLH in years according to sex of the patient is shown in Table 4.17.

TABLE 4.17 Age of onset of XLH in years according to sex of the patients

Age of onset	Male (n= 17)	Female (n=33)
Mean (in years) $\pm$ SD	1.89 $\pm$ 1.1	2.08 $\pm$ 1.63
Range (in years)	0.5 to 4.0	0.25 to 9.0
95% CI	1.32 to 2.46	1.5 to 2.6

The age of onset in male and female patients were compared by using the unpaired t-test. It was found that there was no significant difference between the two groups ($p=0.74$).

4.4.4.4 Ethnic distribution

The age of onset of XLH in subjects of different ethnic group is shown in Table 4.18.

TABLE 4.18 Age of onset of XLH in years according to ethnicity

Age of onset	Asian (n=2)	Black (n=31)	White (n=17)
Mean (in years) $\pm$ SD	1.25*	2.37 $\pm$ 1.7	1.4 $\pm$ 0.66
Range (in years)	1.0 to 1.5	0.25 to 9.0	0.5 to 3.0
95% CI	*	1.7 to 3.0	1.1 to 1.7

* Standard deviation (SD) and 95% confidence interval (CI) for Asian were not calculated due to small sample size.

The age of onset in black and white patients were compared (Asians were excluded due to the small sample size) by using the unpaired t-test. It was found that there was a significant difference between the two groups ($p<0.03$) with white subjects having a significantly earlier age of onset than black subjects.

4.4.4.5 Summary

The subjects with the hereditary type of XLH and white subjects appeared to have a significantly earlier age of onset of disease than those with the sporadic type and black subjects respectively. However, there was no significant difference in age of

onset between the affected male and female subjects.

4.4.5 EXPRESSION OF XLH

4.4.5.1 Introduction

Attempts were made to determine if the sex or ethnic group of the affected individual or the type of mutation played any role in the severity of the disorder. The anthropometric measurements (height z-score), biochemical parameters (serum phosphate, TRP, TmP/GFR and ALP) and radiological features recorded at the time of presentation were compared in males and females, black and white subjects and those with hereditary and sporadic types of XLH.

4.4.5.2 Anthropometric measurement

Anthropometric measurements (at presentation) in different XLH subgroups are shown in Table 4.19.

TABLE 4.19 Anthropometric measurements (at presentation)* in different XLH subgroups

	Sporadic	Hereditary	p value	Male	Female	p value	Black	White	p value
Height z-score	-3.82 ± 1.36 (20)	-3.01 ± 1.53 (15)	0.10	-3.84 ± 1.3 (15)	-3.19 ± 1.55 (20)	0.19	-3.79 ± 1.43 (12)	-2.39 ± 1.07 (3)	0.01
Head circumference z-score	-0.15 ± 1.52 (12)	0.73 ± 1.2 (3)	0.37	-0.27 ± 1.5 (7)	0.41 ± 1.4 (7)	0.41	-0.37 ± 1.38 (8)	0.48 ± 1.53 (7)	0.28

*Values are expressed as the mean ± SD; the number of subjects are provided below in brackets;

The anthropometric data were compared by using the unpaired t-test among the XLH subgroups of interest: male and female, black and white, sporadic and hereditary types. Measurements were taken at the time of presentation. No significant difference was found in head circumference z-score between the different subgroups. However, the height z-score was significantly different between the black and white subjects and white subjects were taller than the black subjects but these data was available for only three white subjects. There was no difference in anthropometric measurements between male and female, and sporadic and hereditary cases.

4.4.5.3 Biochemistry

Biochemical findings (at presentation) before onset of treatment between different subgroups of subjects with XLH are shown in Table 4.20.

The biochemical data were compared by unpaired t-test among the subgroups of interest: male and female, black and white, sporadic and hereditary cases. No significant difference was found in any of the biochemical test results between different XLH subgroups.

TABLE 4.20 Biochemical findings* (at presentation) in different XLH subgroups

	Sporadic	Hereditary	p value	Male	Female	p value	Black	White	p value
Serum ionised Ca	1.21 ± 0.02 (6)	1.20 ± 0.05 (3)	0.76	1.21 ± 0.04 (5)	1.20 ± 0.03 (4)	0.92	**	**	**
Serum total Ca	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 phosphorus	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	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	70.05 ± 22.85 (16)	78.25 ± 12.15 (10)	0.30	71.9 ± 18.2 (10)	73.9 ± 20.9 (16)	0.80	**	**	**
TmP/GFR	0.64 ± 0.23 (14)	0.73 ± 0.22 (10)	0.37	0.61 ± 0.18 (9)	0.72 ± 0.25 (15)	0.29	**	**	**

*Values are expressed as the mean ± SD; the number of subjects are provided below in brackets;

** calculations are not done because they are very few results.

4.4.5.4 Radiology

The radiological findings for the lower extremities (at the time of presentation) were compared among: male and female, black and white subjects, and in the sporadic and

hereditary cases. No significant difference was found for any radiological features between the different subgroups of subjects.

4.4.6 SUMMARY

The data for the genetic study were collected from the review of the records of 50 patients. Additional information was obtained from interviews of the parents of 26 patients who came to the clinic during the period of study. The analysis of the pedigrees showed that the disorder was more common in females than males (the sex ratio was 2.1). The sporadic type of XLH was slightly but not significantly more common than the hereditary type. The sporadic type also appeared to be more prevalent in the black population, although there was no statistically significant differences between the two groups. The subjects with the hereditary type of XLH had an earlier onset of the disorder than did those with the sporadic type. The white subjects appeared to have an earlier onset of the disorder than black subjects had. The height z-score was significantly different between the black and white subjects and white subjects were taller than the black subjects. However, there was no difference between male and female, and sporadic and hereditary cases. No significant difference was found for any biochemical test results or for radiological features, at the time of presentation, between the different subgroups of subjects. This might possibly due to the small sample size or because there was no actual difference in these subgroups.

4.5 PSYCHOSOCIAL STUDY

4.5.1 INTRODUCTION

For the psychosocial part of the study, parents and older patients (16 years or older) were asked to participate when they attended the MMRU clinic for follow-up. The parents of 20 (40%) patients and 7 older patients came to the clinic during the period of study and agreed to participate. Also in one subject, both the affected person and his parent were interviewed separately. All the subjects were interviewed regarding their psychosocial problems using the specially constructed schedule of questions.

4.5.2 BIOGRAPHY

4.5.2.1 Introduction

The first part of the schedule was concerned with the personal details of the subjects and their parents. The aim was to obtain information on the education, occupation, marital status, and socio-economic status of the parents and older patients (more than 16 years of age).

4.5.2.2 Biographical details of patients with XLH

Information was obtained from the parents of the affected child in 20 subjects and the affected persons themselves in seven subjects on the age, sex, ethnic group, and level of education of the patients. The details are shown in Table 4.21. The age range of the patients at the time of interview was 1.08 to 41 years and seven of them were more than 16 years. There were 18 female and 8 males. The majority of the patients were black (20), four were white and only two subjects were of Asian origin. Eleven patients did not have any education (four were too young to attend school), 12 were at school and three had tertiary education.

TABLE 4.21 Characteristics of patients with XLH

Characteristics	Subjects
Total number of affected individual	26
Females	18 (69%)
Males	8 (21%)
Age in years	
Mean	14.65
Range	1.08 to 41.00
More than 16 years	7
Ethnic group	
Asian	2
Black	20
White	4

4.5.2.3 Biographical details of parents

Information was obtained from the 20 parents, who were interviewed on their own regarding their ethnic group, level of education, occupation, socio-economic status, and the age of the parents at the time of birth of their affected child. The details are shown in Table 4.22.

TABLE 4.22 Characteristics of parents who were interviewed

Characteristics	Subjects	
	Number	(%)
Total number of parents interviewed	20	
Fathers	5	25%
Mothers	15	75%
Ethnic group		
Black	17	85%
Caucasoid	2	10%
Asian	1	5%
Social class		
Class II	4	20%
Class III NM	3	15%
Class III M	2	10%
Class IV	3	15%
Class V	5	25%
Unemployed	3	15%
Married	15	(75%)
	Father Number and (%)	Mother Number and (%)
Level of Education		
Not educated	2 (10%)	3 (15%)
School education	16 (80%)	14 (70%)
Tertiary education	2 (10%)	3 (15%)

Altogether 15 mothers and 5 fathers were interviewed. The majority of them were black (17, 85%), two (10%) were of white and only one (5%) was of Asian origin.

At the time of birth of the patients, the mean age of the fathers and mothers were 32 years and 29 years respectively. The majority of the parents were married (15, 75%); two (10%) were living with partners and three (15%) were single. Most of the parents had attended school but there were two (10%) fathers and three (15%) mothers who had no education at all.

The occupations of the parents (who were interviewed) of 20 children were varied. Among the 20 fathers, four (20%) were unemployed, four (20%) unskilled workers, four (20%) partly skilled workers, one (5%) skilled manual worker and three (15%) skilled non-manual worker and four (20%) managerial and professional workers. Among the 20 mothers, 12 (60%) were unemployed, one (5%) unskilled worker, one (5%) partly skilled worker, one (5%) skilled manual worker, three (15%) skilled non-manual workers and two (10%) managerial and professional workers. The social classes were assessed on the basis of the parents' employment and classified according to the higher of the two parents' occupation (OPCS, 1986).

4.5.2.4 Summary

Information was obtained from the parents of the affected child in 20 subjects and the affected persons themselves in 7 subjects. The age range of the patients at the time of interview was 1.08 to 41 years. Seven of them were more than 16 years. The majority of the patients were female (69%) and most of them were black (20, 77%). The majority of them were attending school. The parents were from different socio-economic classes and most of them had some schooling. The average age of the father at the birth of the affected child was 32 years and of mothers 29 years.

4.5.3 PERCEPTION OF THE CAUSES OF XLH

Information was obtained from the parents about their perception and knowledge of XLH. All the parents were questioned about the cause of XLH and their perception of the hereditary nature of the disorder.

The parents' beliefs about the cause of XLH prior to their attending the MMRU or SAIMR clinics are shown in Table 4.23. Most parents believed that the causes of

XLH were environmental rather than genetic.

TABLE 4.23 Parents' initial belief about the causes of XLH

Causes	Number of subjects and (%) (N =20)
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%)

Parents were then asked about their current perception of the causes of XLH. There were 10 (50%) parents who said that they knew about the hereditary nature of the condition. These parents were asked about who they thought transmitted the disorder. The responses were as follows: seven (70%) said that they transmitted the disorder; two (20%) said that their partners transmitted the disorder; and one (10%) said that she did not know.

After explaining the hereditary nature of the condition, the parents were asked if they would be relieved, if the nature of the condition was not inherited. All the parents (20, 100%) responded affirmatively.

It was apparent from the above findings that parents did not have a clear understanding of the hereditary nature of the condition prior to attending a clinic where XLH and its inheritance were discussed. However, after attending such a clinic, the hereditary nature of the disorder was still not clear to 50% of the parents.

4.5.4 REPRODUCTIVE ATTITUDE

Information was obtained from the parents about their attitudes to reproduction with particular reference to prenatal diagnosis for XLH (if such a test were available in future and termination of pregnancy, if the fetus tested positive).

4.5.4.1 Future pregnancies

Parents were asked if they would like to have any more children and 50% of the parents answered affirmatively.

4.5.4.2 Prenatal diagnosis and termination: of pregnancy

Parents were asked if they would choose to have prenatal diagnosis (if it was available in future). Seventeen (85%) of the parents said they would like to have prenatal diagnosis, so that they could prepare themselves for having an affected child and the treatment could be started earlier. Parents were also asked, if they would request termination of the pregnancy (TOP), if the fetus was found to have XLH. Only 2 (10%) of the parents answered affirmatively since they did not want to have another deformed child. Eighteen (90%) said that they would not request termination, as they felt that the condition was not life-threatening.

4.5.4.3 Summary

The majority (85%) of the parents would choose to have prenatal diagnosis. However, only a few (10%) of them would act on the basis of a positive result and request a termination of pregnancy.

4.5.5 PSYCHOLOGICAL ASPECTS OF PHYSICAL DISABILITY

The parents were asked about the main deformities resulting from XLH in their children, their effects on the child's life, as well as on their family activities.

4.5.5.1 Main deformities at the time of first presentation

The parents were asked about the deformities that they had initially noticed in their children which had motivated them to bring the child to a clinic or hospital. Their responses are shown in Table 4.24. Some parents reported more than one deformity. Two parents stated that they had brought their children to the clinic, because one of the parents had XLH and they wanted to know if their child was also affected.

TABLE 4.24 Reasons for presenting a child with XLH at a clinic or hospital

Reasons for presentation	Number and (%)
Bowing of legs	19 (95%)
Short stature	5 (25%)
Pain in legs	5 (25%)
Dental problems	3 (15%)
Hereditary	2 10%)

4.5.5.2 Disruption of patients' life

Regarding the effect of the physical deformities of their children on their life and activities the parents reported as follows:

- Fifteen (75%) stated that there were effects and that the child could not walk long distances, could not always attend school, and had prolonged and many hospitalisations;
- Eight (40%) parents said that their children had problems at school due to the inability to walk long distances, inability to play sports, long absences from school because of prolonged stays in hospital, and poor compliance regarding taking of medicine during school hours.

4.5.5.3 Disruption of family life

Parents were asked if physical deformities of their children had caused any disruption in their family life. The answers were as follows:

- 60% of the parents felt that they had disruptions in family life due to loss of income and other financial problems, regular visits to the hospital, and inability to visit friends and relatives as the child could not walk for long distances;
- 50% of the parents claimed that they had to make special arrangements, such as a baby-sitter, and obtain special transport;
- 50% of the parents said that the children were missed by the family members due to their prolonged hospitalisation.

4.5.5.4 Summary

Although XLH is not a life threatening condition, it still affected the life and social activities of families with an affected member, as well as the lives, educational and social activities of the patients themselves.

4.5.6 INTERPERSONAL RELATIONSHIPS

Parents were asked whether the condition had any impact on the interpersonal relationships within the family and with outsiders. They also completed Beck's depression inventory.

4.5.6.1 Family dynamics

The majority of the parents stated that the disorder of their children did not appear to affect the child's relations with the sibs and only one (5%) parent said that her affected child had problems with his siblings due to his physical deformity.

4.5.6.2 Depression of parents

Parents were interviewed using the Beck depression inventory to find out if they were depressed. The results are shown in Table 4.25.

TABLE 4.25 Beck depression inventory score for parents

SCORE	NUMBER OF PARENTS		
	Father (n=5)	Mother (n=15)	Total (n=20)
Median	2	7	4
Range	1 to 2	0 to 14	0 to 14
95% CI	1 to 2	4 to 10	3 to 8

Statistical analysis using Mann-Whitney Test showed that the median of score of the five fathers was significantly lower than that of the 15 mothers ($p=0.04$). It was also found that all the fathers (5, 100%) had score less than 10, while five (33%) mothers had scores above 10 (0-10 indicates no depression and 11-20 indicates mild depression) (Beck, et al., 1974). Thus, it can be concluded that the mothers showed

more depression than the fathers did in this sample.

4.5.6.3 Interactions with others

Only four parents reported that their child's disorder had an effect on relationships with other children. The relationship appeared to be affected by the child's physical deformity, inability to run and short stature.

4.5.6.4 Summary

XLH is a chronic disorder, but it does not necessarily affect the interpersonal relationships of the patients. However, it was also associated with depression in some of the mothers with affected children in the present study.

4.5.7 PSYCHOLOGICAL EFFECTS ON AFFECTED PATIENTS

Seven patients were interviewed who were 16 years or older. Among them six were female and one male. One of them was Asian, four black, and two white. Their mean age was 31 years with a range of 17.8 to 41 years

4.5.7.1 Deformities

Patients were asked to state what their deformities were and their answers are shown in Table 4.26.

TABLE 4.26. Deformities of the patients as reported by themselves

Deformities	Number and %
Bowing of legs	7 (100%)
Pain in legs	6 (86%)
Short stature	4 (57%)
Others	2 (29%)

4.5.7.2 Disruption of life

When asked about their current disabilities, two patients (29%) said that they were

disabled at the time of the interview because of joint pain. They were also asked if XLH had caused any disruption in their lives and the answers are listed in Table 4.27. The findings showed that the disorder had affected their lives particularly due to their inability to walk normally and their constant need for medical attention.

TABLE 4.27 Disruption of life of patients as reported by themselves

Disruption of life	Number and %
Inability to walk long distances	7 (100%)
Regular intake of medicine	7 (100%)
Regular visit to the hospital	5 (71%)
Inability to work	3 (43%)
Prolonged hospitalisation	3 (43%)
Short stature	3 (43%)
Inability to go to school	2 (29%)
Ugly look	1 (14%)

4.5.7.3 Perception and knowledge about the hereditary nature of the condition

When asked about their knowledge about the hereditary nature of the condition, six (86%) patients said that they knew about the hereditary nature of the condition. One of them (14%) said that she knew that she had got the disorder from her mother, and six (86%) said that they knew that they could pass the disorder onto their children.

4.5.7.4 Summary

It was found that the disorder had affected the life of the patients as reported by themselves and all of them felt that their limited ability to walk and necessity to take medicine regularly disrupted their lives. The majority (86%) knew about the hereditary nature of the condition.

4.5.8 GENETIC COUNSELLING IN XLH

Parents were asked how they had received the information about the disorder and its cause and whether they had been counselled about it.

The majority of the parents (18, 90%) said that they first went to their local clinic or

hospital and the doctor told them that their children had rickets and they had to be seen by a specialist physician. Two (10%) of the parents brought their young children directly to MMRU clinic because they knew about the hereditary nature of the condition. Fourteen of the subjects (70%) said that they had seen other people with rickets.

Genetic counselling was described to the subjects and then they were asked if they had received such counselling, and only two (10%) answered affirmatively. The other parents were asked if they were interested in receiving such counselling and 14 (77%) answered affirmatively.

4.5.9 CONTACT WITH OTHER PARENTS AND A SUPPORT GROUP

4.5.9.1 Contact with other parents

Parents were asked whether they had any contact with other parents who had children with XLH and how they experienced this, or if they had not, if they would like to meet other parents. Only eight (40%) of the subjects had had contact with other families who had children with XLH, and they were asked about this experience. Examples of their responses follow:

- 'My sister had an affected child, and it helps because we and our children can relate to each other.'
- 'It is nice to speak to someone in the same position to the one that you are in.'
- 'It was helpful because I have learnt how to cope with a child with XLH from it.'
- 'It was helpful because I have learnt about the problems with a child with XLH from it.'
- 'It was good that I was not alone.'

Those subjects (12, or 60%) who did not have contact were asked whether they would like to meet other parents who had children with XLH. Ten of them (83%) answered affirmatively. Three parents' responses were as follows:

- 'It would be nice to have had support.'
- 'I would like to share and compare our experiences.'
- 'It would be interesting to know that someone else had problems like us.'

4.5.9.2 Support group

The concept of a 'Support Group' was explained and the parents were asked whether they would join a 'XLH Support Group'. Almost all of the parents (18, 90%) answered affirmatively.

4.5.9.3 Summary

About 40% of the parents reported that they had contact with other families and they had benefited from it. The remaining parents did not have contact with other families, but 83% of them would like to meet with other parents. Finally, most of the parents (90%) would like to join a support group.

4.5.10 SUMMARY

The data for the psychosocial section of the study was collected using a schedule of questions in an interview with the parents of 20 patients and with seven older patients (16 years or older). The analysis of the responses to the interview showed that parents did not have a clear understanding of the hereditary nature of XLH prior to attending a MMRU or SAIMR clinic, and even after attending such a clinic, it was still not clear to 50% of the parents.

The majority of the parents stated that they would like to have prenatal diagnosis for XLH in future, but only a few of them would request TOP on the basis of a positive result. Although XLH is not a life threatening condition, it still affected the family life and the lives of the patients as well as the interpersonal relationship of the patients. It was also associated with significantly more depression in mothers than fathers. Altogether, 60% of the parents did not have contacts with other affected families and 83% of these parents would like to have such contact. Finally, most of the parents (90%) would like to join a support group. In view of these findings, referral for proper genetic counselling is necessary for these parents and the older patients, and the establishment of a support group should be considered.

4.6. SUMMARY AND CONCLUSIONS

In this chapter, the results of the data on the clinical, genetic and psychosocial sections of the study are presented. The subjects were 50 patients who were investigated at the clinics of MMRU and SAIMR and some had been attending such clinics over a period of more than twenty years. They originated from northern provinces of South Africa (mainly Gauteng) and the neighbouring countries.

The data for the clinical section of the study were collected from both the files of the 50 subjects and the clinical examinations of 26 of these 50 subjects who came to the clinics during the period of the study. The majority of them were female (33 or 66%) and black (31 or 62%), although 17 (34%) were white and two (4%) Indian. The anthropometric measurements showed that most of the subjects were short and although they tended to get better with treatment, but never reached normal levels. The findings of the clinical examinations showed that main deformities at the time of first presentation at a clinic were deformities of the lower extremities, which had improved significantly with treatment (medical and/or surgical). The serum phosphorus, and ALP values and urinary TRP and TmP/GFR values at first presentation (before onset of treatment) were significantly different from the reference values for normal individuals. However, there were significant improvements in serum phosphorus and ALP values when levels taken at presentation and after 6 months on treatment were compared. There was also significant improvement in the radiological features when these were compared prior to and after treatment. The majority of the patients were treated with phosphate supplementation and vitamin D analogue $1\alpha\text{-OHD}_3$. Poor compliance (58%) with the medical treatment was a major problem. In spite of medical treatment, 70% of the patients had to undergo corrective orthopaedic surgery. Another problem associated with this disorder was prolonged hospital admissions. Few complications, such as hyperparathyroidism and chronic diarrhoea, were found in these subjects.

The data for the genetic section of the study was collected from a review of the records of 50 patients and the interviews with the parents of 20 patients and 7 older patients. The analysis of the findings showed that the disorder was more common in

females (sex ratio 2:1). The sporadic type of mutation was slightly commoner than the hereditary type. However, sporadic type was more common in black subjects. The subjects with hereditary type of XLH appeared to have earlier onset of the disorder than did those with the sporadic type. The white subjects appeared to have an earlier onset of the symptoms of the disorder than black subjects had. Sex, ethnic group and type of mutation (sporadic or hereditary) in the proband did not influence the expression of the disorder in these subjects except that white subjects were taller than black subjects were.

The data for the psychosocial section of the study were collected during interviews with the parents of 20 patients and seven older patients (16 years or more) themselves who came to the clinic during the period of study. They were from different ethnic groups and socio-economic classes. The findings showed that parents did not have a clear understanding of the hereditary nature of the condition even after attending the clinics of MMRU or SAIMR. Most of the parents stated that they would like to have prenatal diagnosis in future pregnancies whereas only a few (2, 10%) of them would consider a termination of pregnancy for an affected fetus. Although XLH is not a life threatening condition, it still affected the family life and social activities and disrupted the lives of the patients. It was associated with significantly more depression in the mothers than the fathers. The majority (60%) of the parents did not have contacts with other affected families and most of them like to have such contact. Finally, most of the parents (90%) would join a support group, if one was available. Most parents would also like to be referred for comprehensive genetic counselling.

CHAPTER 5

DISCUSSION

5.1 INTRODUCTION

In this chapter, the results obtained from the analysis of the data will be discussed and compared with those from other published studies. Furthermore, in some instances the researcher will attempt to explain the findings according to his own hypothesis. Although not every aspect of the findings will be discussed in this chapter, selected topics from the three sections of the study will be covered.

5.2 THE SAMPLE

5.2.1 SAMPLE SIZE

The subjects for the retrospective part of the study were ascertained from the lists of patients seen at the clinics of the MMRU at Chris Hani Baragwanath Hospital and Johannesburg Hospital, as well as the genetic counselling clinic of the SAIMR. The sample size was 50 XLH patients from 40 families and their records were obtained and reviewed. The ethnic mix was similar to that of the general population in Gauteng and the other northern provinces of the country.

However, the sample size for the prospective part of the study was smaller. Only, 26 out of possible 50 (52%) patients were examined and parents of 20 patients were interviewed. Owing to the fact that patients had attended clinics over a period of more than twenty years, and they came from different geographical areas, it was not possible to find and/or contact all of them. For the same reasons, only seven out of the 30 (24%) older patients were interviewed. Although, the sample size was small, it nevertheless provided some insight into the psychosocial problems associated with the disorder. Other researches have also used small samples in some cases. For example, Rivkees, El-Hajj-Fulehman and Brown, et al. (1992) studied the complications of high dose of phosphate therapy in three XLH patients, and Friedman et al. (1993)

studied the effect of $1,25(\text{OH})_2\text{D}_3$ and phosphate therapy on 12 patients with XLH. In comparison, Whyte et al. (1996) studied the effect of gender, race, anticipation and parent of origin on disease expression in a bigger sample of 116 children by reviewing data over a period of twelve years. Econs et al. (1994) studied perception and knowledge of XLH, using a specially constructed questionnaire, which was sent to 234 subjects (including 57 affected people and 177 family members of the affected people). Although the sample size of this study is small, the MMRU is the only place in the northern part of South Africa to hold clinics for patients with XLH. Therefore, the sample probably represented the maximum number of accessible patients. In addition, one of the purposes of this project was to undertake a basic descriptive study and identify possible areas of research on XLH patients in South Africa. Therefore, the small sample size was thought to be adequate for this purpose especially considering the time constraints on the project.

5.2.2 CHARACTERISTICS OF THE SAMPLE FOR THE PSYCHOSOCIAL STUDY

The subjects for the psychosocial section of the study consisted of the parents of 20 patients who came to the clinic during the time period under investigation. They were interviewed together with seven older patients (16 years or older). Among the parents, there were fifteen mothers and five fathers and the majority (17 or 85%) of them were black. Although they were from various socio-economic classes, there were only four parents (20%) in the social class II. Kromberg and Berkowitz (1986) studied 241 patients attending genetic counselling clinics in Johannesburg and found 40% of the female patients occupied professional or managerial positions (class I or II). In the present study, most of the subjects had some school education but 10% of the fathers and 15% of the mothers had never attended school. This figure is similar to that shown in 1996 Government census, which reported that 10% of the population had no education (Central Statistical Service, 1997).

5.3. CLINICAL STUDY

5.3.1 CLINICAL PRESENTATION

The mean age of onset of XLH in the patients studied was 2.02 years. This is similar to the age of onset data presented by Carpenter (1997). He stated that XLH patients typically present with their first symptom in the second or third year of life.

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. Similarly, Orstavik, et al. (1996) mentioned that the most common manifestations in children were bowing of the lower extremities, short stature and rickets. Abnormalities of the upper extremities were less commonly found in other studies (Orstavik, et al., 1996) and found only in 4% of the subjects in the present study. Econs, et al. (1994) mentioned other clinical features such as bone pain, dental abscess, and abnormalities of the skull (e.g. scaphocephaly), which were also found in some of the subjects in the present study. Dental manifestations in XLH have been usually reported in older children and adult patients with XLH (Seow, et al., 1995; Yamamoto, 1997). In the present study, dental problems were present in 8% of the patients.

Five patients with XLH brought their newborn children to the clinic probably because they were aware of their own problems and did not want their children to suffer like themselves, and therefore, they requested early diagnosis and treatment. The remaining parents (18 or 78%), who were XLH patients themselves, did not bring their children for a check-up immediately after birth, they waited till the children started showing features of XLH, like bowing of the legs. This was probably due to their lack of knowledge about the hereditary nature of the condition, and indicates that parents should be made aware of this aspect of XLH and the implications for their children.

A problem of continuing concern for XLH children is that most of them never achieve normal height. However, several investigators have found that normal growth can be maintained for long periods by regular intake of phosphate and 1α -OHD₃ (Glorieux,

et al., 1980; Rasmussen, et al, 1994). Clinical examination of the patients in the present study showed that 12 (71%) boys and 14 (42%) girls were below the fifth centile of the height/ age at the time presentation. Although, their height tended to improve with treatment, it remained significantly lower than normal.

The commonest deformities at the time of first presentation in the present study were of varus deformities of the lower extremities (80%). The other deformities included those of the upper extremities, skull and chest. These deformities improved significantly after treatment. No cardiovascular or renal abnormalities were found in patients with XLH in the present study. The most common manifestations reported in adult patients are osteomalacia, dental disease and osteoarthritis (Orstavik, et al., 1996) and in the present study features of osteomalacia were present in two adult subjects.

5.3.2 BIOCHEMICAL PARAMETERS

XLH is biochemically characterised by hypophosphatemia, normocalcemia, normal plasma intact PTH, and inappropriately low 1,25-(OH)₂D₃ and renal phosphate wasting (Rasmussen, et al., 1994; Econs, et al., 1994; Carpenter, 1997).

In the present study, it was found that ionised and total calcium, magnesium levels and calcium creatinine ratio in urine were normal at presentation (before onset of treatment) and did not change after 6 and 12 months of treatment. These findings are consistent with the findings of the other studies (Rasmussen, et al., 1994; Carpenter, 1997).

The major biochemical abnormality in XLH patients is hypophosphatemia. The low TRP and TmP/GFR in the setting of hypophosphatemia, document the inappropriate renal phosphate losses characteristic of XLH (Rasmussen, et al., 1994; Carpenter, 1997). In every instance in which it has been studied, the hypophosphatemia in XLH has been associated with increased renal excretion and decreased net renal tubular reabsorption of phosphate resulting in low TmP/GFR values (Carpenter, 1997). Rasmussen, et al. (1994) found values ranged from 50-87 $\mu\text{mol/dl}$ (0.5-0.87 mmol/l)

in adult patients compared with a mean value in normal persons of approximately 1.4-1.8 mmol/l. In the present study, serum phosphorus, TRP and TmP/GFR values were significantly lower than normal at presentation as expected in XLH patients.

The main cause of hypophosphatemia in patients with XLH is renal phosphate wasting, and the therapy with phosphate never corrects that defect, it only increases the serum phosphorus level during therapy. In addition, serum phosphorus levels fluctuate depending on the time interval between ingestion of phosphate and collection of blood. Therefore, serum phosphorus as well as TRP and TmP/GFR (as they are dependent on serum phosphorus level) are not good monitors for evaluation of treatment (Glorieux, Chabot and Tau, 1991). In the present study, serum phosphorus levels increased significantly from the values found before onset of treatment to 6 months after treatment ($p < 0.0001$), as well as 12 months after treatment ($p < 0.0001$), and at the last visit ($p < 0.01$) but in the majority of patients still remained lower than normal.

In children with XLH, total alkaline phosphatase (ALP) activity is usually elevated and remains high in affected individuals with evident rickets. This is unlike most other forms of rickets where treatment results in rapid fall in ALP. This is probably due to following reasons: (1) continuing osteomalacia despite radiological healing of rickets and (2) failure to obtain adequate healing of the rachitic lesions, as the treatment can not completely cure the disease (Rasmussen, et al., 1994). Therefore, monitoring ALP levels is not a particularly sensitive indicator of response to therapy, particularly in adults (Carpenter, 1997). In the present study, ALP values were elevated before onset of treatment ($p < 0.0001$) but there were significant improvements in serum ALP values after 12 months of treatment ($p < 0.001$), although the values in the majority of patients (79%) did not return to normal.

Carpenter (1997) recommended a secondary level of investigations, such as serum intact PTH and vitamin D metabolites i.e. 25-OHD₃ and 1,25-(OH)₂D₃, to confirm the diagnosis. The serum concentration of intact PTH has been measured by number of investigators and several groups have reported low, normal or elevated levels in untreated subjects (Arnaud, Glorieux, and Sriver, 1972; Lewy, Cabana and Repetto, et al., 1972; Reitz and Weinstein, 1973; Rasmussen, et al., 1994). The development of

hyperparathyroidism is one of the complications of therapy. Although elevated parathyroid values were common during treatment, only one patient (2%) had developed hyperparathyroidism in the present study. Statistical analysis showed that mean serum intact PTH values of the subjects at presentation (before onset of treatment) were no different from normal ($p=0.8$). Serum intact PTH was not routinely tested in these subjects. Therefore, in the present study, it was not possible to compare the values of serum intact PTH before and during treatment. Characteristically, 25-OHD₃ levels are normal in subjects with XLH, distinguishing the disorder from vitamin D deficiency (Haddad, et al., 1973; Carpenter, 1997). In the present study, statistical analysis showed that mean 25-OHD₃ levels of the subjects before onset of treatment were no different from normal ($p=0.16$). Circulating 1,25-(OH)₂D₃ levels are also normal in subjects with XLH but inappropriately so given the ambient hypophosphatemia, which normally serves to increase circulating levels of this metabolite (Glorieux, 1980). In this study, statistical analysis showed that mean 1,25-(OH)₂D₃ levels of the subjects before onset of treatment, were no different from normal ($p=0.77$).

In general, the biochemical findings of this study are comparable to those of other studies, and the serum phosphorus levels improved significantly with treatment.

5.3.3 RADIOLOGICAL FEATURES

Radiologically, XLH is characterised by evidence of rickets without features of osteopenia (Carpenter, 1997; Pettifor, 1998). This is associated with osteomalacia, which may become symptomatic in later life (Rasmussen, et al., 1994). The rachitic abnormalities are most apparent in the legs, but in more severely affected individuals, the upper limbs may also be involved. In the present study, radiological examination of the lower extremities showed that the majority of the patients (95%) had radiological features suggestive of rickets and 93% of those patients improved with treatment. The radiological examinations of the upper extremities showed that 40% patients had features suggestive of rickets and 87% of those patients improved with treatment. Once epiphyseal closure has occurred, many patients with skeletal deformity and short stature do well with no specific therapy, show no evidence of osteomalacia on radiological examination, in spite of continued histological

osteomalacia. Other adults may show continued bony changes on X-ray including osteomalacia and pseudofractures. In the present study, two patients had radiological features suggestive of osteomalacia at 30 and 32 years of age respectively.

5.3.4 TREATMENT

The treatment of XLH is aimed at correcting the hypophosphatemia, improving growth, and reducing the severity of the bone deformities and resulting activity limitations. At present, combined therapy of phosphate and calcitriol or 1α -OHD₃ is the best approach (Rasmussen, et al., 1994; Pettifor, 1998). The majority of patients in the present study were treated with phosphate supplementation and the vitamin D analogue 1α -OHD₃.

Compliance with the medical treatment of a chronic disorder is a universal problem. It might seem reasonable to assume that a patient given a prescription will obtain the medicine and actually consume it. The rate of non-presentation has been estimated at 1-5%. But further, having obtained the medicine, some 40-50% of patients do not accurately follow prescribers' instructions or do not take it at all (Laurence and Bennett, 1992). In the present study, there was poor compliance (58%) with the treatment regimen. Regular long-term intake of medication is the mainstay of treatment. However, that was a major problem in the present study group, particularly in school going children and patients from remote areas. Problems were aggravated by the non-availability of medicine (as phosphate and 1α -OHD₃ were not on the essential drug list) in hospitals without any specialists. The patients had to come to an academic hospital to collect the medicine every month, which presented a major stumbling block. Only the very few patients who had medical aid could afford to get a regular supply of medicine without attending an academic hospital. The patients with XLH were usually seen at the MMRU clinics once in every 3 to 6 months. As a result, it was not possible to monitor patients regularly. The inclusion of the two essential drugs on the 'Essential Drug List' might be helpful in increasing their availability in remote areas. The situation is even more hopeless for patients outside South Africa, where these drugs are not available. In this study, 70% of the patients had to undergo corrective orthopaedic surgery partly due to these problems.

5.4 GENETIC STUDY

5.4.1 PATTERN OF INHERITANCE

From the pedigree analysis of patients with XLH, the incidence of sporadic and hereditary type of mutations was calculated as 46% and 54% respectively. 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 also possible that there are other mechanisms involved in those sporadic cases, such as non-paternity, non-penetrance, phenocopy and autosomal recessive inheritance. It is then problematic to decide what the a priori risk that an isolated case has resulted from a new mutation or other mechanisms is or whether it has been transmitted, and what the recurrence risks for the mother's future children are. In future molecular studies might be helpful in this situation.

In the present study, there were more females (66%) than males (34%) as is expected in an X-linked dominant disorder like XLH. It was the impression of the staff of the MMRU that the sporadic form of the disorder was more common in black than white subjects, however this was not supported by the findings in this study. Although the sporadic type was more common in black (20/31, 64%) than white patients (7/17, 41%), no statistically significant difference was found.

5.4.2 AGE OF ONSET OF SYMPTOMS

The patients with the hereditary type of XLH had an earlier age of onset of the disorder than did those with the sporadic type ($p < 0.05$). Also, white patients had a significantly ($p < 0.03$) earlier onset of the disorder than did the black patients. One probable explanation for these findings is that patients with the hereditary type of XLH and white subjects had more severe form of disorder. Another possible explanation is that white patients were identified earlier than black patients due to their better health awareness and the accessibility of health services (which in the past were more easily available to the former group) and other socioeconomic factors. No differences were found when the age of onset in male and female patients were

compared. These factors have not apparently been recorded in any previous studies and need further investigations in a larger sample.

5.4.3 SEVERITY OF THE DISEASE

Whyte, et al. (1996) investigating 116 patients, failed to show any evidence that the sex or ethnicity of the patients affected the expression of the gene for XLH. They used data for height, dietary calcium, and biochemical parameters like serum calcium (total and ionised), phosphorus, ALP, intact PTH, urinary phosphorus/creatinine ratio and Ca/Cr ratio, and lastly TRP and TmP/GFR. They also compared these parameters in patients with hereditary or sporadic form 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 blood biochemistry [serum Ca (total and ionised), magnesium, phosphorus, ALP, intact PTH, vitamin 25-OHD and 1,25-(OH)₂D₃ and TRP and TmP/GFR] or radiological features were found between the male and female, black and white patients or those with the hereditary or sporadic forms of XLH. 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. The explanations for higher height z-score in white subjects might be: (1) the white patients might seek treatment earlier and more compliant with treatment or (2) in general, the white subjects are taller than the black subjects possibly due to better nutritional status. The relatively small numbers of patients in each subgroup meant that these data could not be tested statistically for significance.

5.5 PSYCHOSOCIAL STUDY

5.5.1 PERCEPTION AND KNOWLEDGE OF XLH

The findings of this study showed that most of the parents did not have a clear understanding of the hereditary nature of the condition prior to attending a clinic at MMRU or SAIMR. However, after attending a clinic, it was still not clear to 50% of the parents. Econs, et al. (1994) found that despite the presence of XLH in family members, most of the affected individuals had little or no knowledge about the

disease. They concluded that the lack of knowledge in the parents might be due to their limited access to medical care, their forgetting that they were 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 patients and lack of proper referral to available services might play a role in this regard.

5.5.2 REPRODUCTIVE ATTITUDE

The majority (85%) of the parents said they would like to have prenatal diagnosis for XLH in future pregnancies, so that they could prepare themselves and treatment could be started earlier in the affected infants. However, only two (10%) of these parents stated that they would request a termination of pregnancy if the fetus tested positive, because they did not want another deformed child. These parents were unemployed, not married and, therefore, social factors might have played a major role in their decision. Those 18 (90%) parents, who said that they would not request termination of pregnancy for an affected fetus, added that they felt that the condition was not life threatening.

5.5.3 PSYCHOSOCIAL ASPECTS PHYSICAL DISABILITY

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. In the present study, the main deformities of the patients at the time of presentation (according to parents) were bowing of the legs, short stature and pain in legs. The resulting physical deformities may challenge some basic suppositions associated with the normal look and stature of people, and some of the psychological aspects of self might be profoundly violated. Langer (1994) mentioned that the losses incurred in disability, broadly defined, whether minimal or major, physical, psychological, symbolic, or all of the above, may lead to some predictable human emotional responses, although individual patient's and their parents' responses vary. Therefore, the deformities associated with XLH and possible stigmatisation of affected people should be taken into consideration while counselling patients and their families.

The majority of the parents (15, 75%) said that the physical deformities of their children had caused disruption in their lives and eight (40%) parents said that their children had problems in schools. The physical deformities of the children had also caused disruption in their family life. Some problems were associated with financial issues, such as special transport being requested, loss of income of parents (who had to bring the child 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 like 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 (Macleod, et al., 1998). It is necessary to evaluate the quality of life of the XLH patients by assessing their external conditions, interpersonal and personal psychological conditions, for the provision of a better counselling service and before planning any intervention programme for patients with XLH and their families.

5.5.4 INTERPERSONAL RELATIONSHIPS

XLH is associated with psychological and psychosocial as well as clinical problems for the affected person and his or her family. The family members of a person with physical disabilities are part of a family unit whose balance, functioning and development have been disrupted (Padrone, 1994). However, in the present study, although parents described many different family problems, only one parent stated that her affected child had a difficult relationship with a sibling, partly due to his physical deformities.

Several studies have found that various aspects of a disabled child's condition indirectly affected the mother's psychological functioning, via a direct effect on mother's role functioning, and resulting in deterioration of maternal mental health and depression (Dytrych, et al., 1991; Fisman, et al., 1991; Waddington, et al., 1992; Lambrenos, et al., 1996). In the present study, some (5, 33%) of the 15 mothers interviewed were found to have mild depression, but none of the five father showed any depression according to the results obtained on the Beck depression inventory.

Although this is only a trend in a small sample, Fisman, et al. (1991) also found that the stress generated by affected children had less impact on paternal than maternal psychological health.

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. Within this family climate, the risks for emotional and behavioural problems in the siblings should be evaluated, along with their intrinsic strengths, to plan preventive interventions for these children. Parental adjustment is also an important outcome in child disability interventions, as well as an important mediating variable for other child and family outcomes (Pal, et al., 1998). These factors 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.

Varni et al. (1991) investigated a group of children with congenital or acquired limb deficiencies. They found that social support from classmate, parent, and teacher, peer acceptance, scholastic and athletic competence accounted for 78% of the variance in perceived physical appearance in those children. In the present study, parents were asked if the disorder of their children had any effect on the child's relationship with other children. Four (20%) parents 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 with appropriate education of the teachers about XLH.

5.5.5 PSYCHOLOGICAL EFFECTS ON PATIENTS

No study could be found which had aimed to investigate the psychosocial aspects of XLH on adult patients. As they grew older, their paediatrician 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 patients. 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 (Thompson, 1990, Varni, et al., 1992).

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

5.5.6 GENETIC COUNSELLING IN XLH

Health professionals, like genetic counsellors, play a key role in health promotion by encouraging effective coping in disabled children and members of their families, and by incorporating psychosocial interventions into their practice (Carlson, et al., 1990). Only 10% of the parents had received genetic counselling in the present study, which might be the reason for their lack of knowledge about the hereditary nature of the condition. However, this poor genetic knowledge could also be due to poor communication and to language and cultural barriers between the parents and with the medical professionals who treat them. Krauss, Mars and Lachman (1994) conducted a cross-cultural retrospective study in Cape Town to investigate the problems parents experience when told that their child is physically and/or mentally disabled and found that use of a language other than the parent's tongue tends to have a negative influence on the communication between doctors and parents. The affected individuals and their parents should be made aware of the hereditary nature of their disorder, the recurrence risks, and possibility of prenatal diagnosis in order to facilitate family planning, early diagnosis and treatment of their future affected children.

5.6 SUMMARY AND CONCLUSIONS

From the discussion, it appears that the findings of this study are generally similar to those reported by other authors. For example, there were more affected females than males as expected in a X-linked dominant disorder; there was significant hypophosphatemia, and low TRP and Tmp/GFR levels in these patients as expected in XLH; the majority of patients had rickets at presentation, but radiological features improved significantly with treatment. However, there are some unusual features. Firstly, the patients with the hereditary form of XLH appeared to have a significantly

($p < 0.05$) earlier age of onset of the disorder than did those with the sporadic form. Secondly, white subjects had a significantly ($p < 0.03$) earlier age of onset of the disorder and higher height z-scores than did black subjects. Lastly, the psychosocial study provides a new focus for research on XLH patients and sheds light on their psychological, social and family problems. For example, it was found in the present study that: the hereditary nature of this condition was only understood by half of the parents; XLH as a chronic disorder had not only affected the family life but also disrupted the lives of the patients. Hopefully, the findings from this study will enlighten help genetic counsellors as well as other health professionals so that they can provide a better counselling service to XLH patients and their families.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

In this chapter the results will be assessed in relation to the aims of the study, so that conclusions can be drawn. The limitations of the study will be analysed and recommendations will be made with reference to the findings of the study. These recommendations will focus on provision of appropriate management of XLH patients and their families. Finally, ideas for further research will be presented.

6.2 CONCLUSIONS RELATED TO THE AIMS OF THE STUDY

The broad objective of this study was to investigate a series of XLH patients, to study the pattern of clinical presentation, some aspects the genetics, and some of the perceptions and psychosocial problems associated with XLH. The study was divided into three separate sections: clinical, genetic and psychosocial. The key findings from the study are reported below in these three sections of the study.

6.2.1 CLINICAL STUDY

The objective of the clinical study was to investigate in a South African group of subjects: the clinical picture of the patients, the changes in biochemical parameters and the radiological features over time (at diagnosis and during treatment) and presence of complications.

The majority of affected patients initially presented at the clinic due to bowing of their legs. The findings of the clinical examination showed that the main problems were deformities of lower extremities and short stature.

The findings of this study showed that the majority of the patients were treated with phosphate supplementation and vitamin D analogue $1\alpha\text{-OHD}_3$ which is now accepted

as standard treatment for XLH all over the world (Latta, et al., 1993; Carpenter, 1997; Pettifor, 1998). Compliance with medical treatment appears to be a major problem in most of the patients (29/50, 58%). This problem was compounded by the lack of regular supply of the medicines in the rural areas. Poor compliance could necessitate surgery. Another problem associated with XLH was the prolonged hospitalisation of the patients. This is very costly for the Department of Health, as well as affecting the family dynamics as mentioned in the psychosocial section. Therefore, the Department of Health should consider extending both the regular supply of medication and the genetic counselling services from the cities to the rural areas to improve management of XLH patients and reduce their morbidity.

The radiological findings showed that the features of rickets was present both in the lower extremities (95%) and upper extremities (40%) and majority of them improved with treatment. These findings were similar to those of other studies (Carpenter, 1997; Pettifor, 1998) and they indicate that radiological examinations of the lower and upper extremities are invaluable tools in making a diagnosis and evaluating treatment.

In the present study very few patients had complications like hyperparathyroidism (1, 2%).

6.2.2 GENETIC STUDY

In the genetic study, the aim was to investigate the family history, the pattern of inheritance, the numbers of sporadic and hereditary types of XLH cases and whether there were ethnic and/or sex differences in the type of inheritance, age of onset and clinical presentation. The results showed that the mode of inheritance in the hereditary cases was X-linked dominant, as expected; there was a sex ratio of two affected females to one affected male; the age of onset of symptoms was earlier in white than in black patients and in hereditary than sporadic cases; but there was no ethnic or sex difference in type of inheritance or clinical presentation except that white subjects appeared to be taller than black subjects.

6.2.3 PSYCHOSOCIAL STUDY

The aim of this section was to investigate some of the psychosocial factors associated with XLH and the needs, and problems of the affected patients, and of parents with an affected child, as well as attitudes towards prenatal diagnosis, and lastly, their perceptions, and myths about the disorder.

The majority of the parents (85%) stated that they would request prenatal diagnosis in future pregnancies, whereas only a few (10%) would act on the basis of the result and request termination of pregnancy for an affected fetus. From this result, it can be concluded that: the perception is that XLH is not life threatening; parents may only wish to have prenatal diagnosis, so that they can prepare themselves for having an affected child; and they therefore require a comprehensive genetic counselling and prenatal counselling service, so that they can make their future family plans in an informed way.

Some mothers of the affected children in the present study showed a mild form of depression, which was probably never diagnosed and not treated. Such depression can lead to poor coping with the affected child and therefore it should be recognised. When these families are counselled, mothers should be carefully observed and referred for expert help, if such depression is suspected.

The seven older patients were interviewed who reported that the disorder had affected their lives detrimentally. These patients should be followed, since their transition to adulthood can be difficult and they may need expert guidance to improve their coping mechanisms in late adolescence and as adults.

Most of the parents had not had genetic counselling and they did not fully understand the genetics of XLH. The conclusion that can be drawn from these findings is that a proper referral system should be put in place so that families at risk for a child with XLH, and those that have such a child can make use of the genetic counselling clinics available at SAIMR and Chris Hani Baragwanath Hospital. Possibly more than one session is required and an informed translator or a counsellor fluent in the patients' home language should be used.

6.3 LIMITATIONS OF THE STUDY

The present study was affected by various limitations described below.

1. A part of the study was retrospective. The collection of data from past records was inadequate due to loss of some records and the fact that some of the patients' records were not properly documented or incomplete.
2. The tracing of all the possible patients was difficult due to their mobility and change of address. Some of the patients lived far from Johannesburg and some were from neighbouring countries and could not participate.
3. The small sample size probably represents the main limitation of the study, since the findings might not be suitable for generalisation to a larger series of patients and their families.
4. The information that was gathered for the psychosocial study relied on parental and patient's self-reports, their perceptions, and memories, which could have been inaccurate (for example, regarding the age of onset of their children's disorder). Also they might not have remembered their past experiences and feelings, and their perception could have distorted the facts over time. However, this is a limitation applicable to many such psychosocial studies.
5. There are also limitations in obtaining data through the use of a schedule of questions. When using a schedule of questions in a face-to-face interview, the interviewer could have influenced the respondents by verbal as well as non-verbal means (Gochros, 1988). The translation of questions from English to other languages might also affect the meaning of the questions, and therefore, the responses might not have been as relevant as they should have been.

6.4 RECOMMENDATIONS

The recommendations made below are based on the findings from this study. Some of the points have been taken directly from suggestions or requests made by the subjects, while others have been determined based on the analysis of the data by researcher. The suggestions and recommendations of the supervisors as well as from members of the audience at the two congresses where this study was presented, were also considered. Possible new topics of research have been suggested. The findings which

the researcher feels would be beneficial and relevant both to the health professionals and to patients are presented below.

6.4.1 REGULAR SUPPLY OF MEDICATION TO PATIENTS

Compliance with the medication was one of the major problems of these patients. This was aggravated by the non-availability of medicine (phosphate and $1\alpha\text{-OHD}_3$ are not on the national essential drug list) in hospitals without any specialists, and irregular visits to specialist clinics. The inclusion of the two necessary drugs on the 'Essential Drug List' might be helpful since they would then be available in all the provincial hospitals even those in remote areas. This will also reduce the travel expenses of the patients.

6.4.2 FOLLOW UP OF PATIENTS AFTER PUBERTY

The paediatrician or other medical practitioners treating a child with a disability and the genetic counsellor offering counselling should focus not only on the physical needs of the child but also on the emotional and social issues associated with being disabled in our society. This dual focus becomes increasingly important as the child matures through adolescence and moves into adulthood. This transition is particularly difficult for an adolescent who is dependent on others for physical care and other independent living skills (Hallum, 1995). Many of the transitional problems faced by disabled adolescents and their parents have roots in early childhood. With an awareness of the specific stressors on the parent caregivers and an understanding of the influence of disability on the developmental processes, the paediatrician or genetic counsellor can play a major role in easing the transition of a disabled adolescent into adulthood. By guiding the parents of a young child through the important tasks of childhood and adolescence, the health professional can set the stage for both the parents and their disabled children to have independent, yet supported lives, focused not on the disability but on mutual respect and life satisfaction. It is recommended that disabled teens and young adults be given more help in independence skills, personal counselling services should be made available, and the genetic counsellor should give teenage-appropriate information about XLH and its side effects. There are also needs

for sex education, and preparation for parenthood. The disabled person should learn both to challenge societal beliefs that strength, independence, and appearance are the essential aspects of a quality life and to encourage belief in the importance of being kind, intelligent, and productive to one's potential capacity.

6.4.3 MOLECULAR STUDY OF THE PHEX GENE

The molecular study of PHEX gene is a prerequisite to the ability to confirm the sporadic and hereditary forms of XLH. In addition, molecular studies will identify the different types of mutations of the PHEX gene, which occur in the different ethnic groups in South Africa. If some common mutations can be found, then it will be possible to offer molecular testing to confirm the diagnosis in some doubtful cases and in prenatal diagnosis. In this study, the majority of the parents (85%) said that they would like to have a prenatal diagnosis, so this service would probably be used if it were made available.

6.4.4 SCREENING OF CHILDREN OF PARENTS WITH XLH

There is a need to screen all the high-risk newborn babies of mothers with XLH and daughters of fathers with XLH with the aim of early institution of therapy to prevent the development of serious degrees of deformity. However, the age at which hypophosphatemia first appears is variable. Harrison, Harrison and Lipshitz, et al. (1966) have reported normophosphatemia from birth to six months or later in children who then developed hypophosphatemia, growth retardation and rickets. In the present study, the earliest age of onset was three months. Therefore, it can be concluded that infants at risk should be examined at birth and then every three months thereafter, and treatment should be started when hypophosphatemia appears.

6.4.5 THE GENETIC COUNSELLING SERVICES FOR FAMILIES WITH A MEMBER WITH XLH

The few parents who were exposed to genetic counselling found it worthwhile. Most parents had only a limited knowledge of the genetics of XLH, and therefore, it is important that the families with children with XLH receive such counselling. As one

subject stated regarding her counselling experience:

‘After the counselling I had answers to a lot of previously unanswered questions’.

Genetic counselling for XLH, like any other inherited disorder, should be provided in a non-directive manner, following the internationally accepted aims of genetic counselling and should address the following aspects:

1. The medical and social aspects: these include an explanation of the diagnosis and prognosis, the features, associated physical disabilities, and treatment options including the importance of good compliance with the drug regimen, and possible psychosocial problems;
2. The genetic aspects: XLH is a relatively unknown disorder and parents need to understand the inheritance pattern and the nature of the gene defects. As XLH is inherited in an X-linked dominant fashion there are implications for future children and other family members. The risks to offspring and other relatives of having a child with XLH need to be explained clearly to the parents;
3. Available options: Parents need to know about all the options (such as prenatal diagnosis, if it becomes available) so that they can make informed decisions about future child bearing;
4. Emotional support: The parents need to receive recognition and understanding of their emotional issues associated with a having a child with a physical disability. Empathic counselling should be provided in at least one or two follow up sessions after initial counselling.

6.4.6 FORMATION OF A SUPPORT GROUP

The present study found that the majority of the parents with a child with XLH would like to meet other parents and they would join a support group. Such a group can provide emotional and psychological support, socialising opportunities, valuable information about XLH and educational and other resources, and it can act on special needs of the children and may even improve compliance with medication. Also by working together families and professionals can use the media and improve community attitudes toward children with special needs. In starting a support group, several aspects should be considered. Initially a motivated person, preferably a parent, is needed to get the group going, and time must be allowed for the parents to get

actively involved. A need assessment should be conducted among the family members and the type of group, i.e. family alone or family and professionals should be considered. The purpose of the support group would be (Girson, 1995):

1. To allow families with a common diagnosis to meet and share ideas
2. To help families to understand the special needs of their children and how best to meet those needs
3. To share knowledge regarding community resources to enhance their children's development
4. To receive needed support and knowledge from professional caregivers and other families
5. To assist families in moving beyond their initial reaction after receiving a diagnosis
6. To encourage opportunities for the families to meet in an atmosphere that promotes the sharing of concerns and solutions to problems
7. To provide information about the disorder to members, professionals, and the public.

6.4.7 PUBLIC EDUCATION

A few parents mentioned that doctors and the public were not aware of XLH. Also, for some parents, it took years before they received a diagnosis, which emphasises the fact that information about XLH is probably lacking and should be more readily available. The hereditary forms of rickets are becoming relatively more common as the acquired forms of rickets becoming less frequent (Pettifor, 1998). Therefore, it is a prerequisite to create public awareness about the hereditary form of rickets so that the patients can be managed earlier and in a better way. It is also necessary to educate the parents and teachers about the compliance with treatment, which is absolutely essential for the management of a patient with XLH. It is frustrating for a physician to see a child whose disorder was well controlled and deformity was corrected, returning after some months with a recurrence of the same deformity. Both MMRU and SAIMR as well as support groups (such as Southern African Inherited Disorders Association) could play a part in providing community education. Support group members, in conjunction with experts at academic centres and at the Department of Health, could draw up and provide informative pamphlets on XLH and circulate them widely. The

support group could also compile a regular newsletter, which would keep members up to date with the new research findings, and members could send information and personal stories to popular magazines. They could also organise regular meetings and awareness days. These activities would not only keep the affected families up to date, but also educate the lay public and health professionals.

6.4.8 COLLABORATION WITH OTHER CENTRES

The majority of the subjects in the present study were from the northern provinces of South Africa. The patients from other parts of the country were excluded because they lived too far away to participate and their records were held at other centres. It is recommended that formal links should be developed with other centres who are managing XLH patients to create a national database for such patients. It is also necessary to raise awareness among medical practitioners so that early and accurate diagnosis and good management of the disorder can be achieved. Lastly, collaboration with other centres around the world which are involved with research in XLH will keep local experts up to date.

6.4.9 FURTHER RESEARCH

The following are the areas of research which the researcher believes are important as the findings would both enlighten health workers in the management of XLH patients and benefit XLH patients by improvement in the provision of service.

- i. A longitudinal study of the XLH patients to assess their clinical and psychosocial issues in adulthood
- ii. A study to investigate the usefulness of new born screening of the infants born to patients with XLH.
- iii. Further investigations into the molecular genetics of the PHEX gene to ascertain the actual number of sporadic and hereditary cases, the type of mutations in different population groups, and the exact function of the PHEX gene products

6.5 SUMMARY AND CONCLUSIONS

The findings of the clinical study showed that the main clinical problems of the patients were deformities of the lower and upper extremities, skull and chest, and short stature. Dental and hearing problems were present in some subjects. Hypophosphatemia and associated renal phosphate wasting also occurred in this group of patients. Radiological features suggestive of rickets in children and osteomalacia (in two adult subjects) were found. Most of the patients improved with medical treatment (phosphate and $1\alpha\text{-OHD}_3$) and surgery, although compliance with treatment was a major problem. Compliance could be improved by regular availability of medicines in remote areas and good counselling.

The findings of the genetic study showed that the female to male ratio was nearly 2:1 as expected in an X-linked dominant disorder. The patients with hereditary form of XLH and white patients had significantly earlier age of onset than did those with sporadic forms and black patients respectively. The comparison of blood biochemistry results and radiological features at the time of presentation showed that there was no evidence for sex, ethnic group and type of mutations (hereditary or sporadic) on XLH expression. However, white subjects appeared to be taller than the black subjects were.

From the results obtained from the psychosocial study, it can be concluded that the parents were not fully aware of the hereditary nature of the condition. The presence of a child with XLH had not only affected the dynamics, social activities and interpersonal relationships of the family, but also the life and social activities of the patients themselves were disrupted. Therefore, genetic counsellors and physicians should be aware of the subtle effects of the disorder on both family relationships and functioning and on the parents' coping pattern.

The findings showed that parents appreciate genetic counselling, and therefore this service should be better advertised and utilised. A parent support group should be initiated for the essential support that can be provided only by a peer group. Information regarding XLH should be made available to the public to raise awareness.

Further research may be conducted to study the long term effect of the disorder in adults, to investigate the usefulness of screening of infants born to patients with XLH, to investigate the nature of the PHEX gene and then using the molecular studies, to ascertain actual number of sporadic and inherited cases, and the type of mutations in different population groups. Better clinical and counselling services should be provided to the families with a child with XLH who have to live with the side-effects of the condition, their problems could be better understood and ameliorated, and the quality of their lives improved. It is also necessary to do long term follow up of XLH patients, so that their needs can be met and they can live their lives to the best of their potential.

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APPENDICES

APPENDIX A

**Letter of approval from the 'Post Graduate Committee' and 'Committee for
Research on Human Subjects (Medical)' of University of Witwatersrand**

12 March 1998

Dr D Basu
Department of Obstetrics and
Gynaecology
Johannesburg Hospital

Dear Dr Basu,

APPROVAL OF PROTOCOL ENTITLED "X-LINKED HYPOPHOSPHATEMIA IN A
SOUTH AFRICAN POPULATION".

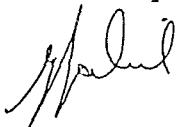
I should like to advise you that the protocol that you have submitted for the degree of MSc(Med)(by coursework and research report) has been approved by the Postgraduate Committee for continuation of candidature. It is noted that ethics clearance for your research is awaited. Please submit a copy of your ethics clearance certificate as soon as it has been obtained.

Professor J Kromberg of the Department of Human Genetics and Professor J Pettifor of the Department of Paediatrics and Child Health have been appointed as your supervisors. You are asked to maintain regular contact with your supervisors who must be kept advised of your progress.

Please note that all candidates for higher degrees must make reference in their research reports to the clearance number of the relevant ethics committee, where applicable. The final title, when submitting the research, should comply with the above approved title, and a signed declaration, noting that the work has been your own and not submitted to any other University, must also be included.

Please also note that Postgraduate students are required to register with the Faculty Office every year until they graduate from the University. Please note, in this regard, that you are not yet registered, as a Study Permit and receipt for fees for the year, must be submitted to me before you may be registered.

Yours sincerely



MRS G GABRIEL
FACULTY OFFICER (POSTGRADUATE)
FACULTY OF HEALTH SCIENCES

cc: Professor JG Kromberg
Professor T Jenkins
Professor J Pettifor

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)

Ref: R14/49 Basu

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M980204

PROJECT

X-Linked Hypophosphatemia In A South African Population

INVESTIGATORS

Dr D Basu

DEPARTMENT

Dept of Human Genetics, Baragwanath Hospital

DATE CONSIDERED

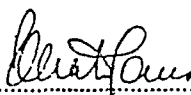
989227

DECISION OF THE COMMITTEE *

Approved unconditionally

DATE 980515

CHAIRMAN.....



(Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Prof JGR Kromberg

Dept of Dept of Human Genetics, Baragwanath Hospital

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DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE SIGNATURE

PROTOCOL NO.: M 980204

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B

Information sheet and consent form

X-LINKED HYPOPHOSPHATEMIA IN A SOUTH AFRICAN POPULATION

PSYCHOSOCIAL STUDY

SUBJECT'S INFORMATION SHEET AND CONSENT FORM FOR PARENTS

X-linked Hypophosphatemia (XLH) is the most common form of familial rickets (bony disease). It usually presents with slow growth, lower limb deformities and low phosphate levels in the blood. Children with this disorder usually develop deformities of the lower limbs (characteristic of rickets) at the time of standing and walking and grow slowly. XLH is transmitted in families and patients with this disorder have about a 50% (1 in 2) risk of having an affected child.

We are interested in studying X-linked hypophosphatemia (XLH) in a South African population, and the impact this disorder has on families of affected individuals.

As the parents of a child with XLH, we would appreciate your help and participation in this study to improve our understanding of the psychosocial factors surrounding this disorder. If you agree to participate, you will be asked to answer a number of questions and to complete a questionnaire about your feelings associated with this disorder. It should not take more than an hour of your time. The results of this study will be analysed, and will be used to improve the services we offer to our patients. This study will not benefit you or your child directly, but it could help others in the future.

Your name, address, and other personal information will be kept confidential and anonymity will be maintained all the time. You do not have to take part in this study, and are free to withdraw at any time without prejudicing the treatment of your child or yourselves in any way.

INFORMED CONSENT:

1. The research (X-linked hypophosphatemia in a South African population) has been explained to me/us. I/we understand that it involves the completion of an interview form or response to questions regarding my/our experiences as parent(s) of a child with X-linked Hypophosphatemia (XLH).
2. I/we understand that while the study may not have any direct benefits for my/our child or me/us, it will help researchers to understand what cause this disorder.
3. I/we understand that my/our name(s), address, and other personal information will be kept confidential to the investigators and anonymity will be maintained all the time.
4. I/we understand that I/we do not have to take part in this project. If I/we choose not to take part, this will not affect the way, in which my child or I will be treated at the hospital/clinic. Similarly, if I/we choose to withdraw from this study at any stage, this will not prejudice any future treatment my/our child or I/we may require.

Child's Name :
Mother's Name: Signature:
Father's Name : Signature:
Address:
Tel No: Contact person:
Hospital: Hospital No:
Date: Study Number:

X-LINKED HYPOPHOSPHATEMIA IN A SOUTH AFRICAN POPULATION

PSYCHOSOCIAL STUDY

SUBJECT'S INFORMATION SHEET AND CONSENT FORM FOR PATIENTS

X-linked Hypophosphatemia (XLH) is the most common form of familial rickets (bony disease). It usually presents with slow growth, lower limb deformities and low phosphate levels in the blood. Children with this disorder usually develop deformities of the lower limbs (characteristic of rickets) at the time of standing and walking and grow slowly. XLH is transmitted in families and patients with this disorder have about a 50% (1 in 2) risk of having an affected child.

We are interested in studying X-linked hypophosphatemia (XLH) in a South African population, and the impact this disorder has on families of affected individuals.

As a patient with XLH, we would appreciate your help and participation in this study to improve our understanding of the psychosocial factors surrounding this disorder. If you agree to participate, you will be asked to answer a number of questions and to complete a questionnaire about your feelings associated with this disorder. It should not take more than an hour of your time. The results of this study will be analysed, and will be used to improve the services we offer to our patients. This study will not benefit you directly, but it could help others in the future.

Your name, address, and other personal information will be kept confidential and anonymity will be maintained all the time. You do not have to take part in this study, and are free to withdraw at any time without prejudicing your treatment in any way.

.....

INFORMED CONSENT:

1. The research (X-linked hypophosphatemia in a South African population) has been explained to me. I understand that it involves the completion of an interview form or response to questions regarding my experiences as a patient with X-linked Hypophosphatemia (XLH).
2. I understand that while the study may not have any direct benefits for me, it will help researchers to understand what cause this disorder.
3. I understand that my name, address, and other personal information will be kept confidential to the investigators and anonymity will be maintained all the time.
4. I understand that I do not have to take part in this project. If I choose not to take part, this will not affect the way, in which I will be treated at the hospital/clinic. Similarly, if I choose to withdraw from this study at any stage, this will not prejudice any future treatment I may require.

Patient's Name : Signature

Mother's Name:

Father's Name :

Address:

Tel No: Contact person:

Hospital: Hospital No:

Date: Study Number:

APPENDIX C

Checklist for Clinical and Genetic Studies

BIOCHEMICAL FINDINGS

DATES					
AGE OF THE CHILD					
BLOOD Ca ⁺⁺					
BLOOD Ca (TOTAL)					
BLOOD Mg					
BLOOD PHOSPHATE					
BLOOD ALK. PHOSPHATASE					
BLOOD CREATININE					
BLOOD PARATHYROID					
BLOOD VITD					
URINE PHOSPHATE					
URINE CREATININE					
TRP%					
TmP/GFR					
URINE Ca/ Cr RATIO					

RADIOLOGICAL FINDINGS

DATES					
AGE OF THE CHILD					
WRIST					
KNEE					
OTHERS					

OTHER INVESTIGATIONS

DATES					
AGE OF THE CHILD					

TREATMENTS

DATES				
HOSPITAL ADMISSIONS NO				
HOSPITAL ADMISSIONS DAYS				

DRUGS

HAS THE TREATMENT BEEN STOPPED? YES/NO

IF YES, AT WHAT AGE WAS IT STOPPED? _____

[illegible]

OTHERS:

REMARKS:

**X-LINKED HYPOPHOSPHATEMIA IN A
SOUTH AFRICAN POPULATION**
GENETIC STUDY

STUDY NO: _____

PATIENT'S PARTICULARS

SEX: M/F DOB: _____ AGE: _____

ETHNIC GROUP: W/ B/ C/ I/ OTHERS (please specify) _____

FATHER'S HOME LANGUAGE _____

MOTHER'S HOME LANGUAGE _____

FAMILY HISTORY:

PEDIGREE:

(Interviewer: please draw the pedigree of three generations, if possible, in the space provided below)

REMARKS:

APPENDIX D

Schedule of questions for Psychosocial Study

X-LINKED HYPOPHOSPHATEMIA IN A SOUTH AFRICAN POPULATION

PSYCHOSOCIAL STUDY INTERVIEW FORM

STUDY NO: _____

PATIENT'S PARTICULARS:

SEX: M/F DOB: _____ AGE: _____
FATHER'S AGE AT BIRTH OF THE CHILD _____
MOTHER'S AGE AT BIRTH OF THE CHILD _____
ETHNIC GROUP: W/ B/ C/ I/ Others (specify) _____
FATHER'S HOME LANGUAGE _____
MOTHER'S HOME LANGUAGE _____

SECTION A: TO BE COMPLETED BY THE PARENT

1. Highest level of education attained

Mother:

- ☐ None
- ☐ Std 5 or lower
- ☐ Std 6-10
- ☐ Std 10 passed
- ☐ Technical college
- ☐ Technikon
- ☐ University
- ☐ Other _____

Father:

- ☐ None
- ☐ Std 5 or lower
- ☐ Std 6-10
- ☐ Std 10 passed
- ☐ Technical college
- ☐ Technikon
- ☐ University
- ☐ Other _____

2. Occupation

Mother's Occupation: _____

Father's Occupation: _____

3. Marital status

- ☐ Single
- ☐ Married
- ☐ Others (specify) _____
- ☐ Living with partners
- ☐ Divorced

4. Socio-economic condition

Monthly income _____

Social Status (to be completed by researcher) _____

5. Child's education

Name of school _____

Standard _____

6. What are the deformities of your child?

(Interviewer, please list them according to the severity as the parent thinks)

1. _____
2. _____
3. _____
4. _____
5. _____

7. Do you think this disorder and its management cause disruption in his/her normal life? Yes/ No
If yes, please specify, the type of disruption.

8. Had you ever seen or known children with this problem before you had your child?
Yes/ No. If yes, state who

8. Information received

8.1 Have you ever been told/ heard about this disorder? Yes/ No

8.2 If so, by whom?

☐ Doctor

☐ Nurse

☐ Genetic counsellor

☐ Other Health care professional ☐ Other

8.3 When were you told about this condition?

8.4 If so, what were you told?

9. What did you think causes this problem?

10. Why did you think this problem happened to you?

11 Heredity:

(a) Do you now know that this bone disease can be passed from generation to generation? Yes/ No

(b) Your child may get this disorder from either you or your partner. Who do you think passed this disorder to your child? You/ Your partner/ Not Known

Does your partner agree with your opinion? Yes/ No/ Not Known

(c) Would you be relieved if this disorder is not a hereditary disorder? Yes/ No

12 Would you like to have another child? Yes/ No

If yes, do you think there is a risk for that child to be affected with this problem? Yes/ No

Why?

13 Prenatal diagnosis

It may be possible in future to detect these disorders in the fetus during the antenatal period. If available in future, would you want to have the test in your future pregnancies? Yes/ No.

Why?

14 Termination of pregnancy

Would you request a termination of pregnancy, if the fetus were shown to be affected? Yes/ No

Why?

15. Do you have to make special arrangements for this child? Yes/No

If yes, please specify _____

16. Does this disorder of the child affect your family life? Yes/ No

If yes, please specify _____

17. Does the child have any problem in school? Yes/ No/ Not known

If yes, please specify _____

18. Does the child have any problems with other children? Yes/No/ Not known

If yes, please specify _____

19. Does the child have any problems with other siblings? Yes/No/ Not known

If yes, please specify _____

20. Did you or your spouse have genetic counselling? Yes/ No

(Interviewer: please explain the concept of Genetic Counselling)

If yes, what are your feelings about it? _____

21. Have you been in contact with other parents who also have a XLH child/children? Yes/No.

If yes, what is your feeling about it? _____

If no, would you like to meet other parents? Yes/ No

22. Would you be interested in joining a 'XLH SUPPORT GROUP'? Yes/ No

(Interviewer: please explain the concept of Support Group)

SECTION B: TO BE COMPLETED BY THE PARENT DEPRESSION INVENTORY

Please choose the statement in each group which best describes the way you have been feeling since you found that your child has XLH.

- 1 0 I do not feel sad
- 1 I feel sad
- 2 I am sad all the time and can't snap out of it
- 3 I am so sad or unhappy that I can't stand it

- 2 0 I am not particularly discouraged about the future
 1 I feel discouraged about the future
 2 I feel I have nothing to look forward to
 3 I feel the future is hopeless and that things can not improve
- 3 0 I do not feel like a failure
 1 I feel I have failed more than the average person has
 2 *As I look back on my life all I can see is a lot of failures*
 3 I feel I am a complete failure as a person
- 4 0 I get as much satisfaction out of things as I used to
 1 I do not enjoy things the way I used to
 2 I do not get real satisfaction out of anything more
 3 I am dissatisfied or bored with everything
- 5 0 I do not feel particularly guilty
 1 I feel guilty a good part of the time
 2 I feel quite guilty most of the time
 3 I feel guilty all the time
- 6 0 I do not feel that I am being punished
 1 I feel I may be punished
 2 I expect to be punished
 3 I feel that I am being punished
- 7 0 I do not feel disappointed in myself
 1 I am disappointed in myself
 2 I am disgusted with myself
 3 I hate myself
- 8 0 I do not feel I am worse than anybody else
 1 I am critical of myself for my weakness or mistakes
 2 I blame myself all the time for my faults
 3 I blame myself for everything bad that happens
- 9 0 I never have any thoughts of killing myself
 1 I have thoughts of killing myself but I would never carry them out
 2 I would like to kill myself
 3 I would kill myself if I had a chance
- 10 0 I do not cry any more than usual
 1 I cry more than I used to
 2 I cry all the time now
 3 I used to be able to cry but I now I can not even cry though I want to
- 11 0 I am no more irritated now than I ever am
 1 I get annoyed or irritated more easily than I used to
 2 I feel irritated all the time now
 3 I do not get irritated at all by the things that used to irritate me
- 12 0 I have not lost interest in other people
 1 I am less interested in other people than I used to be
 2 I have lost most of my interest in other people
 3 I have lost all my interest in other people

- 13 0 I make decisions about as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty in making decisions than before
3 I can not make decisions at all anymore
- 14 0 I do not feel I look worse than I used to
1 I am worried that I am looking old and unattractive
2 I feel that there are permanent changes in my appearances that make me look unattractive
3 I believe that I look ugly
- 15 0 I can work about as well as before
1 It takes an extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can not do any work at all
- 16 0 I can sleep as well as usual
1 I do not sleep as I used to
2 I wake up 1-2 earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and can not get back to sleep
- 17 0 I do not get more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything
- 18 0 My appetite is same as before
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite anymore
- 19 0 I have not lost much weight, if any lately
1 I am purposefully trying to lose weight recently
2 I have been able to loose some weight recently
3 I have lost more weight than I expected recently
- 20 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches, and pains or upset stomach or constipation
2 I am very worried about physical problems and it is hard to think of much else
3 I am so worried about my physical problems that I can not think about anything else
- 21 0 I have not noticed any recent changes in my interest in sex
1 I am less interested in sex than I used to
2 I am much less interested in sex now
3 I have lost interest in sex completely

ADDITIONAL COMMENTS

Are there any comments you would like to make about your situation?

SECTION C (TO BE FILLED ONLY BY PATIENTS WHO ARE 16 YEARS OR OLDER)

1. What are your deformities?

(Interviewer, please list them according to the severity as the patient thinks)

1. _____
2. _____
3. _____
4. _____

2. Are you currently disabled by bone or joint disease? Yes / No

Do you think, these disabilities cause disruption to your life? Yes/ No.

If yes, please specify, the type of disruption. _____

3. (a) Do you know that this bone disease can be passed from generation to generation? Yes/ No.

(b). You may get this disorder from your parents. Who do you think, pass this disorder to you? Your mother/ father/ Not known

(c) Do you know that you can pass this disorder to your children? Yes/ No/ Not known

ADDITIONAL COMMENTS

Are there any comments you would like to make about your situation?

THANK YOU FOR YOUR CO-OPERATION IN THIS PROJECT

Author Basu D

Name of thesis X-Linked Hypophosphatemia In A South African Population Basu D 1999

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