Lower extremity features of Velocardiofacial syndrome and other 22q11 deletions

Submitted in pursuit of a Ph.D. degree

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May 2002

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To my dear parents, Labeba and Qasim Al-Khattat

To my learned mentor, Jackie Campbell

To my best friends, Robert Shprintzen and Ayman Metwali

To my God sent inspiration, Yang Chen

Contents

Acknowledgments

I wish to express my deepest gratitude to the many individuals, families and organisations who significantly contributed to this work. My thanks go to Hazel Square, whose difficulty sparked this and other studies and whose charm and delightfulness remains a pleasure to meet. The UK 22q11 support group was instrumental in the conception and the completion of this stage of the study and Julie and Robert Square never withheld their precious support. The VCFS Educational Foundation remains a powerful force in the promotion and dissemination of this and other work related to VCFS to families and professionals. I also wish to thank all my patients and their families for their trust and continued feedback. My appreciation also goes to Professor Peter Scambler for his valuable advice and guidance, Dr Judith Goodship, Dr Elaine Martin and to the department of School Nurses at Northampton General Hospital.

I am indeed indebted to my personal friends Michelle Denby, Christine Cummenal and Mohammad Nadeem Sayd for being there during good as well as difficult times and for the tremendous support they always lent me.

Finally, I could not thank my partner, Yang Chen, enough for her patience, wisdom and love.

Abstract

This study investigated the symptom of recurrent leg pain of unknown aetiology (PUA) in children and adolescents with 22q11 deletion. A leg pain questionnaire was designed and administered to 300 patients with 22q11 deletion and to 4507 school children. Replies were received from 119 patients (Return rate 39.6%) and from 1391 school children (Return rate 30.8%). A standard battery of clinical tests was applied to 108 patients with 22q11 deletion and mechanical therapy of diagnosed biomechanical foot abnormalities was instituted.

The prevalences of PUA, sleep disturbance and exercise intolerance were found to be significantly higher in patients with 22q11 deletion compared with children of the general population. The clinical picture of PUA is reported and the previously unrecorded association between PUA, sleep disturbance and exercise intolerance is demonstrated in patients with 22q11 deletion. The implications of the differences in the clinical picture and the symptom association between the two populations are discussed. The ages of 8-9 years and 12-13 years emerged as periods during which a possible significant change may occur leading to a dramatic change in the prevalence of PUA, sleep disturbance and exercise intolerance.

The clinical study reports the prevalence of biomechanical foot abnormalities in children with 22q11 deletion and presents evidence of the efficacy of mechanical therapy in alleviating patient' symptoms. The association between biomechanical foot abnormalities and PUA, sleep disturbance and exercise intolerance is explored. This work suggests a possible multifactorial aetiology for the symptoms of PUA, sleep disturbance and exercise intolerance in patients with 22q11 deletion and recommends biomechanical assessment and mechanical therapy if appropriate for symptomatic patients.

Chapter 1

Introduction

In July 1995 a 5-year-old female child with a diagnosis of Velocardiofacial Syndrome (VCFS) was examined at Stantonbury Community Podiatry Clinic, Milton Keynes, UK. This patient attended the clinic for the treatment of curly toes and traumatic blistering of the dorsum of some of her lesser toes; she also suffered from recurrent episodes of leg pain. General Practitioners (GPs) and paediatricians examined the patient and found no discernible reason for such pain; she was diagnosed with "Growing Pain" and subsequently discharged. Further consultations with the doctors were occasioned by persistence of the pain, similarly failed to yield palpable evidence. It was suggested that the parents were being over-anxious and that their child was not suffering from leg pain.

Further enquiries revealed that the patient's mother, one of the organisers of the UK 22q11 support group, is familiar with-at the very least- 4 other VCFS children who suffer similar episodes of leg pain. The patient was invited to attend the Northampton School of Podiatry Clinic in the UK in order to assess her lower limb biomechanical status in search of a possible reason for the leg pain. By July 1997, 12 VCFS patients were biomechanically assessed and attendant podiatric treatment of the ascertained biomechanical lower limb abnormalities was executed with a favourable outcome.

During the course of this preliminary investigation, a number of important and interesting questions and observations emerged. The first obvious question was: were those children actually experiencing leg pain or were the parents as over-anxious as their doctors suggested? This was soon resolved when almost all of the 12 patients who received mechanical therapy for diagnosed biomechanical foot abnormalities registered, what the parents described as, "a very noticeable improvement" in leg pain episodes. The significant observation the parents volunteered was that the children were sleeping better and walking longer than previously since they had started using the insoles.

Whether this favourable outcome constituted valid evidence or the produce of parental wishful thinking remained at that stage debatable since only a small number of closely communicating, albeit geographically disjointed, families were involved. It was, quite rightly, suggested by many professionals that muscular

aches and pains are very common in children in general. These episodes are usually mild and self-limiting and there is no reason to believe that children with 22q11 deletion are any more susceptible to such episodes than those without such a deletion. Hence the primary objective of this investigation: an examination of the prevalence of recurrent episodes of leg pain of unknown aetiology in both children with 22q11 deletion and in those from the general population in order to ascertain whether the pain was more common in the former than the latter.

The absence of any ascertainable cause for such recurrent leg pain episodes lent validity to growing pain as a reliable diagnosis. However, parents declared that their other non-VCFS children had, in their view, experienced growing pain which presented different symptoms from those experienced by their VCFS siblings. This necessitated an examination of the difference between the characteristics of recurrent leg pain in children with 22q11 deletion and their counterparts who do not have this genetic defect.

The interesting observation volunteered by parents regarding better sleep and longer walks since the commencement of mechanical therapy raised a very important question: does mechanical therapy really improve sleep and exercise performance in children with 22q11 deletion? And if so, why? It was therefore necessary to investigate not only episodes of leg pain of unknown aetiology, but also recurrent episodes of sleep disturbance and intolerance to physical exercise.

In 1997, a basic questionnaire was distributed to 150 families of children with 22q11 deletion; it revealed that 54% of the respondents experienced recurrent episodes of leg pain. The need for a more detailed questionnaire became manifest since, firstly, the published medical literature did not contain any studies of recurrent leg pain in children with 22q11 deletion and, secondly, more than half of the respondents to this preliminary survey experienced such recurrent episodes. Similarly, surveying children from the general population became increasingly important since medical literature contained not only scarce but conflicting reports on recurrent leg pain in children, often termed growing pain. General population studies on sleep disturbance and exercise intolerance in children from the general population were even scarcer, more conflicting and more confusing.

Another important phenomenon emerged during the early stages of the preliminary investigation. Some children who did not report leg pain were examined due to recurrent episodes of sleep disturbance or exercise intolerance, or both. What is remarkable is that mechanical therapy of diagnosed biomechanical lower limb abnormalities in these children caused an improvement in their symptoms, although they had never complained of leg pain previously. Hence the possibility that, children with 22q11 deletion were not reporting existing pain, especially since many parents were unable to locate the onset of these leg pain episodes; indeed many parents thought that these episodes might have been present, albeit undetected for some time. A methodology had to be designed to examine such a possibility.

Whereas exercise intolerance was interpreted as individual child laziness, psychiatric problems, bad dreams, attention seeking and further unknown causes were blamed for the continued manifestation of sleep disturbance. Laziness revealed itself as an erroneous interpretation since many children were able to participate un-problematically in lengthy dancing sessions and various sporting activities although a short walk to the market or to school was accompanied by complaints of leg pain, demands for a rest, lagging behind or even crying. The need to consider psychological factors was beginning to emerge. More importantly and confusingly, mechanical therapy improved exercise performance during previously challenging short walks.

The above events suggested that biomechanical lower limb abnormalities might be the primary or at least a major culprit for all 3 symptoms-leg pain, sleep disturbance and exercise intolerance-especially as mechanical therapy, thought to be the treatment of biomechanical lower limb abnormalities, clearly improved all 3 symptoms in the majority of the 12 patients treated in the course of the preliminary study. While the above suggested the possibility of a comparatively straightforward solution for such complex symptoms, it was necessary to thoroughly investigate this process and provide evidence in its support.

As the investigation continued, it became increasingly apparent that biomechanical lower limb abnormalities were highly unlikely to be the only aetiological factor involved in the pathogenesis of this symptomatology and that later these might even constitute a mere aggravating factor.

Finally, it became obvious that the methodology best designed to investigate these events would eschew the investigation of a specific hypotheses in favour of the exploration of various possibilities emergent from the collected data. The possibilities examined by this research have arisen from the accounts of individual parents and one preliminary study.

Chapter 2

Literature Review

2.1. Aspects of 22q11 deletion

2.1.1. Introduction

Velocardiofacial syndrome (VCFS) is a congenital chromosomal disorder, inherited as an autosomal dominant trait (Driscoll et al 1993). It is named after the most common features originally described in 12 patients (Shprintzen et al 1978), where "velo" refers to the palate as all the patients in this sample had cleft palate, "cardio" refers to the heart as 10 out of the 12 patients suffered a congenital heart disease and "facial" refers to the characteristic facial appearance exhibited by all 12 patients. The disease is also known as Shprintzen syndrome, after Robert J Shprintzen, Professor of Otolaryngology, State University of New York, New York, USA.

The condition results from deletions and microdeletions on the long arm of chromosome 22 (Driscoll et al 1992, Scambler et al 1992, Lindsay et al a: 1995). The phrase "22q11" is used to describe deletions on this particular locus on the 22nd chromosome, "22" being the number of the affected autosome, "q" refers to the long arm of that chromosome and "11" is the particular sub-band where the deletion has occurred.

Deletions and microdeletions within 22q11 may result in a number of clinically overlapping conditions (Lindsay et al b: 1995), each receiving a different diagnostic label. Examples of such conditions include VCFS (Shprintzen et al 1978), DiGeorge syndrome (DGS) (DiGeorge 1968), familial congenital heart disease (Wilson et al 1992), conotruncal anomaly face syndrome (Kinouchi et al 1976, Takao et al 1980, Shimizu et al 1984) and others. The majority of these patients were found to have 22q11 deletion. There is a considerable phenotypic overlap between the various 22q11 syndromes and it has been known that different practitioners' clinical diagnosis might differ concerning the same patient.

In view of the wide-ranging clinical manifestations of this deletion, the acronym "CATCH 22" (Wilson et al 1993) has been coined to highlight each of the following features, which may be found in isolation or in combination, with 22q11 deletion. The acronym stands for Cardiac defect, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcaemia due to 22q11 deletion (the acronym is derived from Joseph Heller's novel "Catch 22" published in 1961).

The implication of this acronym that such conditions share a common genetic aetiology was rejected by Shprintzen (1994), arguing that there is no valid evidence to suggest that VCFS is aetiologically heterogeneous, where as DGS is known to be so. Hall (1993) cited data of Driscoll et al (1993) indicating that VCFS is genetically heterogeneous. Shprintzen (1994) refuted this statement, stating that 100% of patients in his sample had 22q11 deletion. Shprintzen (1996) also felt that this acronym makes a mockery out of a situation that seriously affect the lives of many families.

Patients with VCFS may exhibit one or more of over 180 features reported up to date (VCFS Specialist Fact Sheet, web page). The phenotypic expression of VCFS varies widely between patients (Motzkin et al 1993). Some of the more common features may include cleft palate, congenital heart disease (Young et al 1980; Jedel et al 1992), facial dysmorphism (Arvystas & Shprintzen 1984; Lipson et al 1991), hypoplasia or aplasia of the thymus and/or the parathyroid gland (Scire et al 1994), learning and social difficulties (Kok & Salmon 1995) and psychiatric disorder (Pulver et al 1994; Weksberg et al 1994).

Until 1978 when Shprintzen et al described the VCFS, most patients who suffered from that syndrome were diagnosed as DGS. DGS is characterised by hypocalcaemia due to hypoplasia of the parathyroid glands, increased susceptibility to infection due to a deficit in T-lymphocytes caused by hypoplasia or aplasia of the thymus gland. Congenital cardiac malformations are frequently seen, particularly affecting the outflow tract. Facial dysmorphism is also a characteristic feature.

DGS is usually sporadic and result from *de novo* 22 deletion. Many authors however, recognised that the variable features resulting from this deletion in members of the same family with a variable phenotype, are behaving as an autosomal dominant trait (Steele et al 1972; Raattikka et al 1981; Atkin et al 1982; Rohn et al 1984; Kappa et al 1988). Stevens et al (1990) suggested that such familial cases should be regarded as VCFS rather than DGS.

There is a considerable phenotypic overlap between VCFS and DGS (Halford et al 1993). It has been suggested that VCFS and DGS represent a spectrum of the same gene defect (Greenberg 1993).

2.1.2. History

In 1965 during a society of paediatric research meeting, the first of a group of clinically and aetiologically overlapping syndromes was announced. Dr Max Cooper presented some of his work on the embryology of chickens, classifying their immune system into a thymic system responsible for cell-mediated immunity and a bursal system responsible for humoral immunity (Cooper et al 1965).

Dr Angelo DiGeorge, an endocrinologist at St Christophers Hospital for Children in Philadelphia, commented on the work of Cooper et al regarding the absence of the thymus gland found in some chick embryos. DiGeorge and his colleague, Dr James Arey, noted the congenital absence of the parathyroid gland in 3 infants who also showed no evidence of thymic tissue. Those infants were proposed to be the human analogue of Cooper's thymectomised chicks. As DiGeorge stated, "The concurrent absence of both structures is not surprising if one recognises that both are derived from common premordia. Furthermore, this association has been previously recorded although its physiologic significance has not been recognised" (Greenberg 1993).

It was Harrington (1929) who first reported the congenital absence of the thymus gland in humans. 30 years later, Lobdell (1959) noted the association of congenital hypoparathyroidism and thymic aplasia. Despite these earlier reports

and the fact that DiGeorge's paper (DiGeorge 1968) was published 9 years after Lobdell's, the association was dubbed DiGeorge Syndrome by Dr Robert A. Good (Taitz et al 1966). Also, Strong (1968) described a familial syndrome with cardiac anomalies, mental deficiency and facial dysmorphism before the recognition of DGS.

In Japan, Kinouchi et al (1976) worked with what they called "Conotruncal anomaly face syndrome". Although this syndrome shows a considerable phenotypic overlap with DGS, the emphasis in the former is focused on the cardiovascular presentation. Shprintzen et al (1978) described the Velocardiofacial syndrome (VCFS), which also shows considerable phenotypic overlap with DGS and conotruncal anomaly face syndrome, with the emphasis being focused on palatal and craniofacial features.

2.1.3. Genetics

Deletions and microdeletions on the long arm of chromosome 22 (22q11) were found to be associated with the majority of patients suffering from these syndromes. De la Chappelle et al (1981) were the first to suggest that DGS may be caused by a chromosome 22 deletion but, partial duplication of the short arm of chromosome 20 (20p) as a possible aetiology could not be ruled out. This suggestion was based upon the clinical diagnosis of DGS in 4 relatives in whom monosomy of 22pter-q11 and 20p duplication was present. Kelley et al (1982) described 3 DGS patients with translocation of 22q11-qter to other chromosomes, corroborating arguments that monosomy 22q11 causes DGS. The progressive improvement of genetic analysis techniques led to further recognition of the significance of 22q11 deletions in the aetiology of DGS.

Greenberg et al (1988) found chromosome 22 abnormalities in 5 out of 27 DGS cases. Wilson et al (1992) reported high resolution banding in 30 of 36 DGS patients.

Carey et al (1992) found 22q11 deletion in 21 of 22 cases of DGS using molecular dosage analysis and Fluorescent In Situ Hybridisation (FISH) with

probes isolated from within the deleted area, giving pooled results of 33, 22q11 deleted patients among a consecutive series of 35 cases. It is now well established that the vast majority of cases result from deletions within chromosome 22q11 (Scambler et al 1991, Driscoll et al 1992, Carey et al 1992).

The phenotypic overlap between VCFS and DGS led to the speculation that these disorders may share a common aetiology. Scambler (1992) presented preliminary evidence that VCFS is associated with 22q11 deletions. Using DNA probes, Kelly et al (1993) found monosomy of 22q11 in all 12 VCFS patients examined in this series. Driscoll et al (1992) detected an interstitial deletion of 22q11 in 3 of 15 VCFS patients. Molecular analysis using DNA probes from the DiGeorge Critical Region (DGCR) within 22q11, detected a deletion in 14 of those 15 patients.

Using 11 short tandem-repeat polymorphic (STRP) markers, Morrow et al (1995) studied 15 VCFS patients and their unaffected parents. Deletions were demonstrated in 82% of those patients. Parental origin of the deleted chromosome had no effect on the phenotype.
Sirotkin et al (1996), noted that because VCFS is a complex disorder with significant variability in phenotype and penetrance, it is likely that a number of genes in the commonly deleted region contribute to the phenotype.

2.1.4. Clinical features

In their original description of VCFS, Shprintzen et al (1978), presented 12 fairly consistent features in their 12 patients sample. Today, 22 years on, these have expanded to 185 recognised clinical abnormalities, affecting almost all body systems (VSFS specialist fact sheet). The incidence of the various clinical features is variable.

Shprintzen et al (1981) reported the following common abnormalities in 39 patients; cleft palate, congenital cardiac disease, typical facies and learning disabilities. Less common features included; microcephaly, mental retardation,

short stature, slender hands and digits, minor auricular anomalies and inguinal hernia.

Fitch et al (1983) found small optic discs and tortuous retinal vessels in a 6 years old VCFS female. Beemer et al (1986) commented on the marked tortuousity of retinal vessels found in some VCFS patients.

Wraith et al (1985), described a male infant with holoprosencephaly and tetralogy of Fallot who died at the age of 32 days. The infant's mother had tetralogy of Fallot, corrected surgically at the age of 12 years. The mother also had a submucous cleft palate and mild mental retardation. The characteristic facial features of VCFS were evident. These included; prominent tubular nose, narrow downward slanting palpebral fissure and a slightly retruded mandible. This paper suggested that the association of Fallot's tetralogy and holoprosencephaly should prompt examination of relatives in search for other signs of VCFS.

Shprintzen et al (1985) claimed that VCFS is the most common syndrome associated with clefting, accounting for 8.1% of children with cleft palate seen in their centre. All cases described in this paper had facial dysmorphism and learning disabilities characterised by difficulty with abstraction, reading and mathematics. Congenital heart disease was found in 82%. Platybasia occurred in 85% and ophthalmic anomalies were observed in 70%. Most patients suffered recurrent infections with T-lymphocyte dysfunction. Nasopharyngoscopy showed lymphoid tissue hypoplasia or aplasia in the vast majority of patients.

Studies estimating the frequency of cardiovascular anomalies at 98% and cleft palate at 82% were questioned by Meinecke et al (1986). They examined a sample of 8 patients diagnosed with VCFS through their characteristic facial appearance, showing only 2 patients suffering from cleft palate and 4 patients with congenital heart disease. They concluded that the overestimation of the incidence of cleft palate and congenital heart disease in VCFS patients resulted from the patients being seen in cleft palate and cardiac centres. They also noted that mental retardation was not present in any of their 8 patients while it was present in all cases of other published studies.

Congenital hypoplasia of the adenoids was reported in 80% of VCFS patients (Williams et al 1987). As the adenoids aid velopharyngeal closure during speech, it was suggested that this feature contributes to the hypernasal speech observed in those patients.

Lipson et al (1991) reported their findings in 38 VCFS patients seen because of hypernasal speech. Congenital heart disease was present in 42% of cases. Cleft palate was found in 57% and velopharyngeal insufficiency (VPI) was observed in 97% of cases. Pharyngeoplasty was performed in 32 of the 38 patients with the results of the surgery described as good. This paper emphasised the frequent delay in the diagnosis and treatment of hypernasal speech and VPI in VCFS patients.

On the basis of 120 patients, the full spectrum of VCFS was reviewed by Goldberg et al (1993). Learning disability, cleft palate and pharyngeal hypotonia were present in 90% or more of the patients; cardiac anomalies in 82%; slender hands and digits in 63%; medial displacement of the internal carotid arteries in 25%; umblical hernia in 23% and hypospadias in 10% of males.

Golding-Cushner et al (1985), described a characteristic personality of VCFS children as blunt or inappropriate affect. They observed that many of these children develop psychiatric illness later in life. Shprintzen et al (1992) suggested that adolescents and adults with VCFS may develop psychiatric disorder. Dunham et al (1992), found that the HP500 sequence, often deleted in VCFS patients, is located within the same 450 kilobases (kb) yeast artificial chromosome (YAC) as the catechol-O-methyltransferase (COMT) gene. Deletion of this gene may cause psychotic illness.

Pulver et al (1994), found a high incidence of psychosis in VCFS patients and their relatives. They suggested that a schizophrenia associated gene may be present on 22q or a DNA rearrangement may be implicated in the aetiology of psychotic illness in these patients. Karayiorgou et al (1995) performed two studies to examine the genetic overlap between schizophrenia and VCFS. They suggested that the area of 22q11 deletion implicated in the aetiology of VCFS

may harbour genetic lesions that increases the susceptibility to schizophrenia. Carlson et al (1997), examined the relationship between psychiatric illness, VCFS and chromosome 22 deletions by evaluating 26 VCFS patients using clinical and molecular genetic methods. There was no correlation between the phenotype and the extent of the 22q11 deletion. The congenital anomalies of VCFS were found to be associated with a high prevalence of bipolar spectrum disorder that also occurred in non-deleted VCFS patients, suggesting a common genetic aetiology. Meningomyelocele (Nickel et al 1994) and cerebellar atrophy (Lynch et al 1995) have also been reported.

Ryan et al (1997) reported a European collaborative study of 558 patients with 22q11 deletions. A 22q11 deletion affecting one parent was detected in 28.4% of the 285 patients in whom parental deletion status was available, although an inherited ascertainment bias could have influenced this work.

Of the 81 parents with demonstrable 22q11 deletion, the sex of the parent with the deletion was known in 79 cases, with 61 maternal and 18 paternal deletions. 158 patients had their height and/or weight below the fifth centile, 57 of those were below the third centile. 44 patients died and of the 29 for whom age of death was available, 16 died within one month and 25 within 6 months due to congenital heart disease. One patient died as a result of a severe immune deficiency. 107 of 338 cases were developmentally normal, although 37 had speech delay. Of 231 patients with abnormal development, 102 had mild delay and 60 had either moderate or severe learning difficulties. 22 of 252 children had behavioural or psychiatric problems, including 2 with episodes of psychosis. 11 of 61 adults had a psychiatric disorder, 4 of whom had at least one episode of psychosis.

Significant cardiac pathology was found in 409 of 554 patients whose cardiac studies were available. The most common cardiac anomalies encountered included Falott tetralogy, ventricular septal defect (VSD), interrupted aortic arch, pulmonary atrasia with VSD and truncus arteriosus.
Otolaryngeal anomalies were observed in 242 of 496 patients. Overt or submucous cleft palate was seen in 72, velopharyngeal insufficiency without cleft

palate was seen in 161 patients. Hearing data were available in 159 patients of whom 52 had abnormal hearing.

49 of 136 patients had renal abnormalities with absent, dysplastic or multicystic kidnys seen in 23 patients, obstructive abnormalities in 14 and vesicoureteric reflux in 6.

Hypocalcaemia was recorded in 203 of 340 patients. 108 of those had a history of seizures 42 of whom had seizures due to hypocalcaemia. Laboratory and clinical immune function and thymus status were available in 218 patients. Major immune function abnormality was only present in 4 of those. Of 548 patients, 94 had minor skeletal abnormalities and 39 had ocular abnormalities.

The authors concluded that their clinical findings were consistent with previous reports with fewer immunologic problems and more renal problems than expected. They recommended therefore, that abdominal ultrasound should be carried out in all patients diagnosed with 22q11 deletions.

What constitutes DGS or VCFS as a clinical diagnosis remains a matter of debate. It appears that patients seen by endocrinologists presenting with parathyroid and/or thymus problems are more likely to be diagnosed as DGS. On the other hand, patients seen by dysmorphologists or maxillofacial specialists are more likely to be diagnosed as VCFS. In real terms, whatever the clinical diagnosis may be, patients will undergo treatment for the features they exhibit, whether these are labelled as DGS or VCFS. The difference in the clinical diagnosis adds to the confusion of the patients' families and professionals alike. Perhaps a clinical diagnosis of Shprintzen syndrome, 22q11 syndrome or any other nomenclature chosen by the academic medical community might put the minds of those who deal with this disease at rest and finally unify the efforts of clinicians and families in managing the problems associated with this condition.

2.2. Leg pain

2.2.1. Introduction

Pain is the primary symptom that instigates people to seek medical treatment (Turk and Melzack 1992) and probably was the initial impulse that sparked mankind to start the science of medicine.

Attempts at defining pain in terms of the precipitating stimulus, the subjective experience or in terms of its outcome produced a number of unsatisfactory definitions. In 1979, the Taxonomy Committee of the International Association for the Study of Pain (IASP) defined pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such a damage" (Merskey 1979).

St Augustin described physical pain as "The greatest evil" highlighting the unpleasant experience of pain. Nevertheless, pain is an essential individual and species-preserving mechanism. To that effect, the poet David Seegal spoke of pain in the early 20th century. He composed:

Pain, messenger of harm
Nature's poignant alarm
Often man's wily friend
To signal means to mend. (Strauss 1968)

Conflicting theories were proposed by different investigators in an attempt to identify the nature of pain. Before Melzack and Wall (1965) proposed their "Gate Control Theory of Pain", two opposing theories were agreeable to most scientists. The "Specificity Theory" (von Frey 1894) proposed that pain is a specific sensory modality, like vision and hearing. It has its own central and peripheral apparatus. The strength of this theory was in its explicit physiological specialisation while its weakness was in its implicit psychological assumption.

The "Pattern Theory" was proposed by Goldscheider (1894), initially one of the champions of von Frey's theory. He was the first to postulate that stimulus intensity and central summation are the critical determinants of pain. The pattern theory explains the sensation of pain in terms of a specific pattern of nerve impulse. Such a pattern will be produced by intense stimulation of non-specific receptors and will travel through non-specific fibres.

Various theories within the framework of Goldscheider concept emerged. Some ignored the fact of physiological specialisation (Nafe 1934; Weddell 1955; Sinclair 1955) and others that stressed central summation mechanisms rather than excessive peripheral stimulation (Livingstone 1941; Hebb 1949; Gerard 1951) as the physiological phenomenon responsible for pain. Central summation and input control were successful in explaining many clinical phenomena associated with pain. The various related theories however, were lacking unity and did not receive adequate experimental verification.

In 1965 Melzack and Wall proposed their 'Gate Control Theory' which was reviewed and modified subsequently (Melzack 1973; Wall 1973; Wall 1974; Wall 1976; Wall 1978). It proposed a gate system that controlled the passage of pain impulses from peripheral nerves to higher centres. The substantia gelatinosa (SG), located in the peripheral part of the dorsal horn of the spinal cord, assumed a gate function that exerted an inhibitory effect on the central transmission (T) cells located in the deeper structures of the dorsal horn. The inhibitory effect of the SG was increased when impulses were received from large diameter (L) fibres and was decreased when impulses were received from small diameter (Aδ and C) fibres. This means that other peripheral nerve fibres that carry information about innocuous events can inhibit spinal cord cells that relay noxious signals. Brain descending control systems also modulated the excitability of the cells that transmit noxious information. The transmission of pain signals to the first central cells is therefore under control that is influenced by peripheral afferents and central efferents.

2.2.2. Causes of lower limb pain

There is a large number of pathological processes and clinical conditions that may cause lower extremity pain. The 'Task Force on Taxonomy' of the 'International Association for the Study of Pain' published a classification of chronic pain syndromes (Merskey and Bogduk 1994). Very few lower extremity chronic pain syndromes were listed in this publication and these were almost entirely neurological in origin. Izzo et al (1996) compiled a partial listing of the different diagnostic entities that may cause lower limb pain. They have arbitrarily classified these entities into 4 different categories which include; neuropathic origin, musculoskletal origin, central origin and miscellaneous. This list is by no means comprehensive. Lower limb pain may occur due to a vast array of causes (A number of these causes need to be discussed in the course of this work).

2.2.2.1. Ischaemic pain

Ischemia is defined as a reduction of the blood supply to an organ or part of the body. Such a reduction may be acute or chronic and vary in severity from mild asymptomatic to severe, associated with excruciating pain, infarction and gangrene. It results from narrowing or obstruction of the artery(s) supplying the affected area.

The character of ischaemic pain may be described as sore, cramping, tight, pressing, throbbing, squeezing, gripping, numbing, aching, heavy or tiring (Melzak 1975). It varies in severity depending upon the degree, nature and onset of ischaemia as well as the degree of patient's tolerance to pain.

Limb pain associated with exercise and relieved by rest is termed "intermittent claudications". Sir Benjamin Brodie first described it in 1846. It reflects partial arterial narrowing rendering blood supply to the limb unsatisfactory for its increased demands during exercise. In the latter stages of intermittent claudications, the pain may occur during rest and the patient may eventually develop gangrene.

Chronic limb ischaemia may lead to the development of trophic changes including loss of hair, brittle nails, delayed healing of wounds and ulceration. The affected limb will feel cold to the examining hand and the arterial pulse may be diminished or even absent. A Doppler is a very useful bedside tool that can localise the pulses, the palpating hand fail to perceive. It can be connected to a computer allowing arterial waveform studies to be performed.

The method by which pain is produced in ischaemic muscles is uncertain, although it is not thought to be related to muscle tension (Dormandy 1983).

2.2.2.2. Restless legs syndrome (RLS)

Willis originally described RLS in 1685 (Ekbom 1960). It is characterised by an unpleasant, creeping, difficult-to-describe, deep sensation in the legs. It usually comes on in the evening while the patient is at rest and walking will generally bring relief (Ekbom 1945, Yunis and Masi 1993). Insomnia is a great problem and needs sympathetic handling.

The syndrome affects up to 5% of the general population. Men and women are equally affected at any age, though it is more common in the elderly (Cybulska and Rucinski 1985). Familial occurrence is poorly documented although an autosomal pattern of inheritance is known (Montlaisir et al 1985).

The disease is associated with pregnancy, iron deficiency anaemia and uraemia. There is a possible association with poliomyelitis, avitaminosis, diabetes, smoking, Parkinson's disease and lengthy exposure to cold (Clough 1987).

There is also an association with fibromyalgia (Yunis and Aldag 1996) and rheumatoid arthritis (Reynolds 1986). The origin of the sensation is not known, although a vascular pathogenesis was suspected by Ekbom (1960) and a central origin was suspected by Akpinar (1982).

Many patients with RLS will not need drug treatment and reassurance and explanation may be all what is required. Others will manage by walking and by frequently moving their feet when the symptoms arise. In a minority of cases, the

syndrome will interrupt the patient's life, making them avoid social engagements. In all cases, doctors should not belittle the patient's complaint (Clough 1987).

Many drugs have been used in the treatment of RLS. These include clonidine (Handworker and Palmer 1985), carbimazipine (Telstaad et al 1984), clonazepam (Montagna et al 1984), tryptophan (Sandyk 1968), iron folate (Ekbom 1960), chlorpromazine (Cybulska and Rusinski 1985), amytriptaline and procaine infusions (Foster 1981) and levodopa (Von Scheele 1986). Only clonazepam and carbimazipine have shown benefit over placebo (Handworker and Palmer 1985; Telstaad et al 1984).

2.2.2.3. Biomechanical foot abnormalities

Pronation is a triplane motion that occur at the subtalar joint. During normal locomotion, the pronation of the subtalar joint causes the foot to become hypermobile, allowing it to adopt the function of a mobile adaptor and help in attenuating the shock of ground contact (Pratt 1989). This permits the foot to conform to the shape of the supporting surface.

Excessive subtalar joint pronation describes either an increase in the degree of pronation or the extension of the pronation state into later part of the step when the subtalar joint should be supinating (Tollafield and Merriman 1995). Abnormal pronation of the foot is defined as abnormal pronation of the entire foot which occurs at the subtalar joint (Steindler 1952).

During static stance, a pronated position of the foot may result in foot and leg fatigue and ligamentous strain (Dunn 1923; Schwartz and Heath 1937; Schreiber and Weinerman 1948). During locomotion, abnormal subtalar joint pronation is responsible for more chronic low grade foot and postural symptomatology than any other type of foot problem (Root et al 1977).

A number of methods may be used to diagnose excessive subtalar joint pronation. Rose et al (1985) described clinical observation of arch height. Jones et al (1989) considered clinical methods of measurement of arch height to be limited since these are subjective. The use of tractographs, goniometers and protractors to measure the angle between the bisection of the back of the leg and the bisection of the back of the heel in various subtalar joint positions was deemed inaccurate by Milgrom et al (1985). Various footprint parameters were used to classify the human foot into various arch heights. These included foot print angle (Schwartz et al 1928), arch index (Cavanagh and Rodgers 1933), footprint index (Irwin 1937), arch length index and truncated arch index (Howes et al 1992). The latter authors concluded that all these arch height indexes are invalid as basis for prediction or categorisation of arch height. Radiography (Cobey and sella 1981) and ultrasound (Hennig and Cavanagh 1985) were also used but these methods are expensive and not widely accessible for that purpose with the added health risk of ionising radiation associated with radiography.

An equinus deformity is a disability in which the individual's safety, stability and comfort of locomotion are impeded (Hillstrom et al 1991) and is associated with foot pathology (Boyd and Bogan 1997). It may be defined as inadequate ankle joint dorsiflexion for normal gait, a condition in which less than 10 degrees of ankle joint dorsiflexion is available when the subtalar joint is in the neutral position, the mid tarsal joint is fully pronated and the knee is fully extended (Tanz 1960; D'Amico 1977; Whitney and Green 1982; Seibel 1988; Hillstrom et al 1991; Downey 1992). Baggett and Young (1993) on the other hand considered the normal non-weight bearing range of motion of the ankle joint to be 0-16.5 degrees while in his review of the literature, Rome (1996) declared a reported range between 8 degrees and 26 degrees.

Ankle equinus may be associated with proximal pathological changes. Hibbs (1914) noted the symptoms associated with such a deformity stating, "These patients suffer from excessive fatigue, pain in the legs often referred to the back, nervousness and mental lassitude".

The degree of ankle joint dorsiflexion can be measured during weight bearing or non-weight bearing. A tractograph or a goniometer is aligned against certain bony landmarks to obtain the degree of ankle joint dorsiflexion. The Silfverskiold test enables the clinician to distinguish between soft tissue ankle equinus and bonny ankle equinus (Silfverskiold 1924). However, many sources of measurement errors exist when measuring the ankle joint range of motion (Wright and Feinstein 1992) and Elveru et al (1988) considered such measurement unreliable.

It is very difficult to accurately measure the range of motion of small joints (Low 1977). Menz (1998) questioned the validity and reliability of measurement methods used in the podiatric biomechanics. It appears therefore that patient care decisions should be based primarily on symptoms not on measurements (Rome 1996).

2.2.2.4. Leg pains in VCFS

In 1996, personal contact with Professor Robert J. Shprintzen of the Velocardiofacial syndrome Educational Foundation, New York, USA and other medical professionals dealing with VCFS patients, revealed that they were unaware that a proportion of VCFS patients experience recurrent episodes of leg pain.

In the same year, personal contact with the New York School of Podiatric Medicine and the Pennsylvania School of Podiatric Medicine, USA, revealed no knowledge of leg pain or lower limb abnormalities in VCFS patients. Literature search revealed no published work that even mentions this symptom in patients with 22q11 deletion

A preliminary study of leg pain in velocardiofacial syndrome (Al-Khattat 1997, unpublished data) described the most common foot biomechanical abnormalities in VCFS children with leg pain. These included excessive subtalar joint pronation (75%), soft tissue ankle equinus (67%) and anterior displacement of the posterior tibial tendon (58%). These findings were based on the clinical examination of 12 VCFS children with no objective measurement of any of these abnormalities. This appears to be the only study of leg pain in VCFS. The study also included a survey of 150, 22q11 deleted patients. It proposed a preliminary prevalence of leg pain in 22q11 deleted patients of 19-54%.

2.2.2.5. Growing pains

Duchamp (1823) observed that a large number of children suffer various muscular aches and pains which are less common in adults. He was the first known to use the term "Growing Pains", assuming that the growth in children, being absent in adults, was the cause of this condition.

Various definitions of this syndrome have been proposed since. Bennie (1894), defined growing pains as " Pains in the limbs caused by and during rapid growth and sometimes so severe as to give rise to growing fever.". He concluded however, that growing pains was vanishing from the realm of pathology through that of fancy and that it existed principally as an article of faith. He implicated excessive use of the legs as a cause of recurrent limb pain in childhood. His conclusions were not based on experimental evidence but rather on personal experience and by what appears to be a biased interpretation of quoted literature.

Brown (1910), did not give a definition of growing pains, but considered it to be the most important symptom that affected children during the growth period. He suggested that strained or relaxed sacro-iliac joints may be a marked factor in causing growing pains. His suggestions were theoretical with no apparent empirical data.

In his investigation of 891 children attending London and Birmingham hospitals, Hawksley (1931) defined growing pains as "Pain in the limbs which could not be explained on any other grounds". He concluded that growing pains were more common in Mediterranean and intermediate anthropological types of children. He suggested that the greater frequency of growing pains in these children was due to metabolic and constitutional factor rather than an increased susceptibility to rheumatism. While this suggestion, regarding rheumatism, may be supported by his statistics (which were in themselves very misleading as presented), there is no evidence in this work to support metabolic and constitutional factors as the only other possible aetiologies of growing pains.

Seven years later, Hawksley (1938) considered the term growing pains to be of an unsatisfactory nature and found no reason to believe that growth is painful. In

this study of 115 children, he proposed a number of growing pains aetiologies. He found the most common causes of growing pains to be postural deformities or minor orthopaedic deformities such as flat feet, knock knees or scoliosis, vague ill-health and emotional strain. These should have been proposed as associations rather than causes, since there was no evidence that such conditions were actually causing the pain. Growing pains was thought not to involve the joints, producing pain of muscular origin, whereas the site of pain in rheumatism was said to be of articular origin.

He concluded that there was no relationship between growing pain and rheumatic fever and that growing pain could usually be diagnosed and treated by ordinary clinical methods. It does not appear that he reached this latter conclusion by applying a treatment protocol to this group of children but rather by assuming an improvement in symptoms when conventional treatment is applied to abnormalities commonly found in this particular sample. Furthermore, it does not seem appropriate to suggest aetiologies for growing pains, having already considered the term to be unsatisfactory.

One year later, Hawksley (1939) again tackled the subject reinforcing his previous conclusions and suggesting that a definition of growing pains must vary with the observer's own individual interpretation.

Seham and Hilbert (1933), defined growing pains as "Vague recurrent afebrile muscular pains". In their conclusion, they state that the term is a misnomer and should be discarded. This was a two year combined clinical and statistical study of myalgia. A questionnaire was administered to 208 children mostly between 9 and 14 years of age. The ten questions included in the questionnaire were not contained in the published paper neither was the diagnostic criteria of growing pains fully explained. The study considered pain of 3 months duration or more to be relevant. 21% gave a positive response of growing pains, according to the undefined author's criteria.

35 children between 6 and 10 years of age were followed up over a period of two years to detect the association of their chronic muscular pains with chronic

infection. All the children were members of a poor social class, mostly immigrants (Italians, Jews, Swedes) and "Nigroes" (sic) and must consequently be considered more susceptible to chronic infection than the general population. The authors confessed that this sample was not a true representative of all children.

It appears that the authors were biased from the outset against the term growing pains. They did not furnish any evidence that proves that growth is not painful. Instead, they tried to include the term growing pains into the general term of "muscular rheumatism" and studied a small sample of susceptible children, attempting to prove that the majority of these children were suffering from pains related to rheumatic disease.

Shapiro (1939) described the clinical features of growing pains from his experience of a non disclosed number of children referred to his Department of Cardiac Activities in Minneapolis for suspicion of rheumatic fever. All those children were proved to be free of rheumatic fever. He did not define the term growing pains and only used it as a commonly used entity, stating that the term was only speculative of the aetiology.

Naish and Apley (1951) objected to the term growing pains on the grounds that the pain occurs most frequently at an age when growth is far from rapid, that the site of pain does not correspond to the sites of maximal growth and that the intermittent nature of growing pains is unlikely to be due to the gradual process of growth.

This study adopted the strict selection criteria of "...a history of pains of at least 3 months duration, not specifically located in the joints and of sufficient severity to cause some interruption of normal activities.". 30 out of 721 school children attending certain school clinics in Bristol fitted the author's criteria for growing pains. The more stringent selection criteria accounts for the comparatively lower measured incidence of growing pains of 4.2%. The age of onset of pain was between 8 and 12 years.

Detailed analysis of 78 children obtained from the field survey and from children referred to the hospital clinic because of limb pain was carried out. Postural defects such as lordosis, pes plannus and scoliosis were fairly common, accounting for just over 50% of an assessed group of 45 children.
Symptomatically, 3 different groups were described:
Group 1 contained only a few children where vague pains affected the limbs and the body. There was no clear cut distinction between diurnal and nocturnal pain in this group.

Group 2 was the largest accounting for 64% of the sample, where the pains were predominantly diurnal and nearly always occurred in the legs and the feet. Common associations in this group included postural defects, emotional disturbances and a strong family history of rheumatic disorder.

In group, 3 accounting for 27%, the pains were predominantly nocturnal. In the few occasions when the pains were diurnal, the pain was severe and of only short duration. There was no apparent relation to exertion, fatigue or faulty posture. Emotional disturbances were distinctly less common than in group 1 and 2. There was however, a strong family history of growing pains. The pains more commonly occurred during wet and cold weather.

The authors claimed that limb pain in childhood comprises more than one single clinical entity and that an important part is played by psychological factors. They recommended that an investigation of such a problem should not be confined to the child, but should also look into familial parallel data. They concluded that the term "growing pain" should be discarded as no demonstrable connection between the pain and the process of normal growth could be found.

Øster and Nielsen (1972) defined growing pains as "Non-articular pain in the extremities without a demonstrable organic basis". In a representative school population sample of 2,178 children aged between 6-19, they proposed an prevalence of growing pains of 12.5% in boys and 18.4% in girls. They concluded that growth, i.e. height, weight and weight/height ratio, did not play any part in the aetiology. They speculated that Growing pain, like abdominal pain

and headache in childhood, may belong to a special emotional familial pattern. They recommended however, that the term should be retained until research is able to elucidate the aetiology and pathogenesis.

Øster (1972) reinforced his previous findings and concluded that recurrent headaches, growing pain and abdominal pains in childhood tend to regress with time or the different forms of pain may be converted into each other. He declared the prognosis to be dubious.

Calabro et al (1976), defined Growing pain as "Recurrent limb pains peculiar to children the certain diagnosis of which can be obtained only by exclusion and careful long term observation.". They based their conclusions on a five years observation of almost 50 children. They proposed a list of differential diagnoses of localised limb pain and generalised muscular pain. They recommended supportive measures and aspirin as an effective treatment, even though aspirin is contraindicated before the age of 12 because of risk of Reye's syndrome .

Peterson (1977) reviewed the literature and warned of the great diagnostic error of making a diagnosis of growing pain while overlooking some serious underlying condition, a concern highlighted by previous authors.
Wersäll (1952) and Brenning (1960), considered growing pains and restless leg syndrome to be identical or related. Ekbom (1945), discussed this question but did not reach any conclusions. 25 years later, Ekbom (1970), wrote that growing pains resembled the painful form of restless legs.

In discussing two case reports, Ekbom (1975), concluded that growing pains and restless legs syndrome were two different conditions. He highlighted the fact that effective therapy based on the understanding of the pathogenesis often has to wait for many years (as for instance with pernicious anaemia).

In an educational review of limb pain in childhood, Sherry (1990), explained that the so called growing pains occurred between the age of 3 and 5. He considered that stretching exercises, reassurance, time and removal of secondary gain are the only measures needed. The paper contained no investigation and no references.

It appears that the author was delivering his own experience through this work. The age range specified is in contradiction to all other work into growing pain and the management proposed does not appear to be based on any experimental evidence.

In their investigation of 2,165 children attending 76 primary and secondary schools in the city of Aberdeen, Abu-Arafeh and Russel (1996) used the term "Recurrent limb pain of unknown aetiology". This was defined as "At least two episodes of limb pain over a one year period, not due to trauma, infection or other specific illness, each episode lasting no more than 72 hours in the absence of local tenderness, swelling, limitation of joint movement or joint hyperextensibility". This definition was derived from different publications and from the authors' own clinical experience.

The prevalence of recurrent limb pain in this sample was found to be 2.6% of the 1,754 respondents, whose mean age was 10.2 years. The authors concluded that recurrent limb pain in childhood is a common cause of limb pain.

They found close clinical and epidemiological similarities between recurrent limb pain and childhood migraine suggesting a common pathogenesis.

This, the most recent study of recurrent limb pain in childhood, is by far the most credible and stringent in its definition. There was no involvement with the question of painful growth but successful attempts to link this condition with similar recurrent syndromes in childhood. Whether a prevalence of 2.6% renders recurrent limb pain in childhood a common condition is a matter for debate. Nevertheless, this work consolidated previous work in recurrent limb pain in childhood and took a very significant step towards the identification of its pathogenesis.

Oberklaid et al studied a sample of 160 children with a mean age of 8.5 years, identified as having growing pains from a sample of a 1605-member community-based cohort, who participated in the Australian Temperament Project. Their criterion for growing pains was based on a parental affirmative response to the

question: "Has your child experienced any pains in the arms, legs or joints in the last 12 months?" The prevalence of growing pains (according to this definition) in this sample was 11.4%. Almost two-thirds of children with growing pains in this sample were able to localise the site of pain and 83% described it as aching in character. Contrary to other studies (Naish & Apley 1951), 53% experienced the pain during the day as well as the night. Children with growing pains were more likely to be rated by their parents as having a negative mood and to be more intense. Statistical tests showed that this was of uncertain clinical significance. Teacher's rating of temperament showed no difference compared with children who did not complain of growing pains.

The authors conclude that the results of this study provide additional evidence of the commonality of these symptoms, their association with other pain syndromes seen in childhood and their association with a constellation of parent-related temperament and behavioural traits. It also supports the notion that there might be something constitutionally different about children with growing pains.

Chapter 3

Methodology

3.1 Introduction

Recurrent limb pain in childhood (RLPC) has long been recognised as a problem, not only troublesome to children but also to parents and professionals. The literature contains conflicting and controversial opinions about this problem, often termed growing pains. Many authors have speculated on aetiology and recommended treatments for RLPC. Only one series however, provided empirical data about the efficacy of one particular method of treatment (Baxter & Dulberg 1988).

Patients with 22q11 deletions who complained of recurrent episodes of leg pain were almost always diagnosed as having growing pains and no treatment was rendered. Because of the persistence of the pain episodes together with the associated sleep disturbance and lack of exercise tolerance, parents continued to seek medical explanation and assistance, with usually no effective treatment.

A preliminary study (Al-Khattat 1997, unpublished data) suggested a high prevalence of RLPC in patients with 22q11 deletions and suggested a possible correlation between the leg pain episodes and biomechanical foot abnormalities. The preliminary study also suggested that the leg pain, sleep disturbance and intolerance to physical exercise might be improved by podiatric treatment of associated biomechanical foot abnormalities.

The methodology of this research project was designed to investigate these claims. While this work is primarily concerned with children and adolescents with 22q11 deletion, it was also necessary to institute studies of the general population for comparison. This was particularly due to the scarce and conflicting general population data concerning RLPC.

This chapter will detail the methods of inquiry adopted in this research project to answer the various questions raised during the course of investigating leg pains in 22q11 deletions.

3.2. Aims

The aims of this research project were to study the prevalence of recurrent leg pain of unknown aetiology (PUA), sleep disturbance and intolerance to physical exercise in patients with 22q11 deletion, to investigate a possible correlation between these symptoms and biomechanical foot abnormalities and to test the efficacy of conventional podiatric treatment of any associated biomechanical foot abnormalities on these symptoms. Similar epidemiological investigation was carried out in the general population to provide the data necessary for comparative purposes, although no clinical study was instituted on children of the general population in the course of this work.

3.3. Objectives

The objectives of this research project were as follows:

1. To investigate the prevalence and characteristics of PUA in patients with 22q11 deletion and to provide epidemiological data concerning this symptom in the general population. This predominantly involved children and adolescents.
2. To investigate the prevalence and characteristics of recurrent episodes of sleep disturbance and recurrent episodes of intolerance to physical exercise and to investigate possible association of these symptoms with PUA. This will primarily involve patients with 22q11 deletion but similar epidemiological data will be generated from the general population.
3. To clinically assess the nature and prevalence of biomechanical foot abnormalities in patients with 22q11 deletions using clinical tools and clinical tests available to most community clinicians.
4. To investigate the efficacy of podiatric treatment on PUA, sleep disturbance and intolerance to physical exercise in patients with 22q11 deletion.

3.4. Materials and Methods

3.4.1. Materials

Two groups of subjects were studied: a group of patients with 22q11 deletion (Patient sample) and a comparable group of general population children (General population sample), abbreviated as Gp.

3.4.1.1. The patient sample

Individuals in this sample were identified through the following sources:

1. UK 22q11 support group, UK.
2. Chelsea and Westminster Hospital VCFS multidisciplinary clinic, London, UK.
3. The department of Human Genetics, University of Newcastle-Upon-Tyne, UK.
4. Personal contact with a group of VCFS parents in Florida, USA.
5. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 4th annual conference, 1998, Harvard University, Boston, USA.
6. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 5th annual conference, 1999, Medical College of Wisconsin, Milwaukee, USA.
7. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 6th annual conference, 2000, Baltimore, USA.
8. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 7th annual conference, 2001, Miami, USA.

3.4.1.2. The general population (Gp) sample

Individuals in this sample represented a population of school attendees and were identified through two sources:

1. The Department of School Nursing at Northampton General Hospital NHS Trust (7 Schools).
2. Personal contact with Dr Elaine Martin, Consultant Community Paediatrician, Sunderland (2 Schools).

The selected schools represented a range of chronological, social and geographical environments. Specific selection from the above sources for both the patient and the Gp samples was made as appropriate for a prevalence study and a clinical study.

3.4.2. Method

The research project contained two studies, a prevalence study and a clinical study. The prevalence study was applied to both samples, while the clinical study was applied to the patient sample only.

An application was submitted to the Medical Ethics Committee (MEC) of Northamptonshire Health Authority, for its consideration and recommendations regarding potential ethical issues within this study. The MEC was satisfied that all ethical issues were adequately addressed and the application was approved on 13 March 1998 (Appendix IX).

3.4.2.1. The prevalence study

The prevalence and characteristics of episodes of recurrent leg pain of unknown aetiology (PUA), recurrent episodes of sleep disturbance and recurrent episodes of exercise intolerance were investigated by a questionnaire survey. This involved both the patient sample and, for providing comparison, the Gp sample.

3.4.2.1.1. Inclusion criteria

3.4.2.1.1.1. The patient sample

The survey included patients with a diagnosis of a 22q11 deletion syndrome, regardless of its clinical denomination, whether VCFS, DGS...etc. The studied age range is 2-20 years old and both genders were included. The questionnaire was administered only to patients who are registered with the UK 22q11 support group. Other sources of patients were not considered to avoid the possibility of any one patient receiving and responding to more than one questionnaire.

3.4.1.1.2. The general population (Gp) sample

This sample included all children attending the following 7 schools in Northamptonshire and 2 schools in Sunderland:

1. Bracken Lease Primary School (Northamptonshire).
2. Bugbrooke Campion Primary School (Northamptonshire).
3. Deanshanger Primary School (Northamptonshire).
4. Duston Eldean Lower School (Northamptonshire).
5. English Martyrs (Sunderland).
6. Kingsthorpe Grove Lower School (Northamptonshire).
7. Pattishall C.E. Primary School (Northamptonshire).
8. Redby (Sunderland).
9. Roade (Northamptonshire).

To avoid potential sample bias the investigator was not involved in the choice of schools to be included in the study. This was left for staff of the department of school nursing at the Northampton General Hospital. A total of 4507 questionnaires were distributed to schoolchildren.

3.4.2.1.2. Exclusion criteria

Responses were excluded under the following conditions:

1. Respondents over 20 years old.
2. Missing date of birth.
3. More than one person responding on one questionnaire.

3.4.2.1.3. Questionnaire administration and collection

All administered questionnaires were accompanied by a letter (Appendix 1). The letter thanked the participants for their co-operation and explained the aims of the study, highlighting the importance of their contribution and the personal and public benefits that may be gained. It also assured participants that their responses are treated with strict confidentiality and that only the investigators will view any received responses.

3.4.2.1.3.1. The patient sample

To avoid breaching patients' confidentiality, the UK 22q11 support group posted the questionnaires to patients on their records. The investigator did not have access to the support group's confidential list of names and addresses of patients. Patients were asked to send their responses back directly to the investigator, in a provided self addressed stamped envelope. Each patient was given the option to provide their name and address if they wished to be contacted for examination and treatment and for possible inclusion in the clinical study.

3.4.2.1.3.2. The general population (Gp) sample

The questionnaires were distributed to children in 7 schools in Northamptonshire by staff of the School Nursing Department of Northampton General Hospital NHS Trust and to 2 schools in Sunderland by Dr Elaine Martin, Consultant Community Paediatrician. Respondents were asked to send the completed questionnaire back in a provided self-addressed stamped envelope.

3.4.2.1.4. The questionnaire

The questionnaire was primarily designed for administration to patients with 22q11 deletion (Appendix II). A slight modification was made in the questionnaire to make it suitable for children of the general population. This was in the form of omitting the first question of the 22q11 deleted version of the questionnaire, which inquires about a diagnosis of a 22q11 deletion syndrome, since most of the general population subjects and their families are unlikely to be familiar with this term. With a documented prevalence of 22q11 deletions of 1 in 5000 (Scambler 1993), the general population sample was not expected to be significantly contaminated with members of the patient group. Furthermore, a proportion of children with 22q11 deletion attend special schools because of their learning disabilities.

The questionnaire was designed to allow easy reading and easy completion. It only contained 5 main questions with sub-categories to respond to in each question. A negative answer to a main question allowed the respondent to ignore the sub-categories of that particular question and to proceed to the next one. The

questions were meant to be direct, unambiguous and the majority were closed, answered by ticking a box indicating a yes or no response. Technical terms were avoided, although terms related to 22q11 deletions had to be used in question 1 of the questionnaire administered to children with 22q11 deletion. It is expected however, that almost all families with a 22q11-deleted member will be familiar with such terms.

Three symptoms were investigated through this questionnaire. These are recurrent leg pain of unknown aetiology (PUA), recurrent episodes of sleep disturbance and intolerance to physical exercise. Previous experience gained through a preliminary study suggested this line of questioning and subsequent piloting indicated a high degree of satisfaction with the various aspects of the questionnaire.

3.4.2.1.5. Piloting

The questionnaire was piloted by sending it to 10 families with 22q11-deleted children together with a scoring sheet (Appendix III) that asked the recipients to comment on five aspects of the questionnaire design and to give a satisfaction score between 1-5 for each aspect. These included; ease of reading, comprehensibility, format, content and length.

3.4.2.1.6. Outcome measures

The prevalence and characteristics of episodes of PUA, sleep disturbance and intolerance to physical exercise were examined and compared between the patient and the Gp sample. The findings of this examination are listed in chapter 4 and discussed in chapter 5.

3.4.2.1.7. Statistical analysis

Data input and storage, statistical analysis and graphs creation were performed using SPSS, version 9, statistical package. All statistical significance was tested at the 5% level ($p </= 0.05$).

3.4.2.2. The clinical study

The clinical study involved the patient group only. Its aims were to clinically examine subjects selected opportunistically to clinically determine the presence or absence of selected biomechanical foot abnormalities and to investigate the effect of conventional podiatric treatment of diagnosed biomechanical foot abnormalities on episodes of leg pain, sleep disturbance and exercise intolerance, when appropriate. An information sheet was designed to inform families of the various aspects of this study and the patient or guardian signed a consent form in the beginning of the interview (Appendix IV). An assessment protocol for subject interview and examination (appendix V) was designed and applied to all subjects included in the clinical study. All subjects were interviewed and examined by the same investigator and although this may introduce an element of observers' bias, it carries the advantage that if such a bias exist it is likely to be uniformly applied to all subjects. A treatment plan was designed and implemented for each individual patient according to currently accepted podiatric practice in the UK.

Leg pain observation diaries (Appendix VIII) were only completed by one parent and were subsequently replaced with a simple treatment feedback form (Appendix VI). These were designed and distributed to patients, to monitor the effect of the treatment on episodes of the leg pain, sleep disturbance and exercise intolerance.

3.4.2.2.1. The Sample

This sample included patients with a diagnosis of a 22q11 deletion syndrome. Any age and both sexes were included. Individuals contained in this sample were identified through the sources listed in section 3.4.1.1.

The study included those with a clinical or a genetic diagnosis of a 22q11 deletion syndrome but excluded those with a known cause of leg pain. It also excluded those with lower limb injuries, surgery or structural abnormalities, like talipes equinovarus as such conditions may influence the type of leg pain under investigation.

3.4.2.2.2. Setting

Patients were interviewed and examined at different venues, depending on geographical accessibility to patients. Venues included:

1. The Northampton School of Podiatry clinic, Northampton, UK.
2. Chelsea and Westminster Hospital VCFS multidisciplinary clinic, London, UK.
3. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 4th annual conference, 1998, Harvard University, Boston, USA.
4. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 5th annual conference, 1999, Medical College of Wisconsin, Milwaukee, USA.
5. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 6th annual conference, 2000, Baltimore, USA.
6. Leg pain clinic following the Velocardiofacial Syndrome Educational Foundation 7th annual conference, 2001, Miami, USA.
7. The department of human genetics, University of Newcastle-Upon-Tyne, UK.
8. Private clinic of Dr. Stuart Goldman DPM, 1999, Florida, USA.
9. A minority were interviewed at their own homes due to inability to attend any of the above venues.

3.4.2.2.3. The assessment protocol

The assessment protocol (Appendix V) was designed to obtain full history from patient and parents and to clinically examine the biomechanical status of the lower limbs. It consisted of two sections: a clinical history section and a clinical assessment section. The protocol was designed in such a way to prompt the clinician to tick certain boxes indicating the presence or absence of certain features in the history and clinical assessment sections with a space for the patient and parents to register any further comments, observations or concerns that were not raised by the clinician. Alphanumeric sections for date of interview, names of patient and parents, patient's date of birth, address, healthcare professionals that

may need to be contacted, description of toe deformities and registration of the degrees of ankle joint dorsiflexion were included in the protocol.

3.4.2.2.3.1. The clinical history section

In the personal history section, the date of the interview and the date of birth were recorded, to calculate the age of the patient at the time of examination. The venue for the interview was specified and the appropriate gender box was ticked. Details of the Patient's General Practitioner (GP) and Paediatrician were sought and the family was offered the option of forwarding an interview report to any organisation they feel appropriate, including social services and the patient's school.

The first question in the clinical history section inquired about a diagnosis of a 22q11 deletion syndrome and about genetic confirmation of such a deletion. The clinical denomination of the condition was recorded for later analysis of the controversy of the various clinical denominations offered by the various clinicians for, what appears to be, different phenotypic expressions of the same condition, 22q11 deletion. The rest of the clinical history section follows the same format as the leg pain questionnaire. All the questions contain a number of boxes to be ticked by the clinician, choosing the appropriate option(s) and some of them allow the registration of an un-offered response.

This standard systematic approach to history taking ensured the uniformity of the collected data and decreased the possibility of heterogeneous interviews.

3.4.2.2.3.2. The clinical assessment section

In this section, the biomechanical status of the patient's lower limbs was assessed. Only selected observations and clinical tests were chosen. The choice of these is based upon the results of the preliminary study (Al-Khattat 1997, unpublished data) and on the ability of most community clinicians to perform a similar assessment. The time consuming full biomechanical assessment used in the preliminary study was not suitable, mainly from the patients prospective, most of whom travelled a long distance to the interview venue.

It was therefore essential to focus the assessment and to only include selected observations that were shown by the preliminary study to be the most common biomechanical foot abnormalities associated with 22q11 deleted patients suffering from recurrent episodes of leg pain.

3.4.2.2.4. Treatment

All prescribed insoles were made at the orthotics laboratory at the Northampton School of Podiatry, by the investigator. The underside of all manufactured insoles was marked "right and left" and a letter (appendix VII) was sent with the insoles to explain the way these should be used.

All patients that showed excessive subtalar joint pronation or other abnormalities that are known to lead to a compensatory excessive subtalar joint pronation were treated with a simple insole. The base of the insole was made of 3 mm open cell polyurethane foam (Poron) as this was shown during the preliminary study to be more tolerated by the patients than non shock absorbing bases, like texon. Poron functional valgus (D) fillers were added to the poron base and the insole was covered with yampi. The thickness of the D-fillers varied between patients and subsequent modification was available, depending on the response.

All patients that showed soft tissue ankle equinus or limb length discrepancy were treated with a heel raise made of poron on a 3 mm poron base and covered with yampi. Patients who showed both the above features, were treated with a combined poron D-filler and poron heel raise on a 3mm poron base and covered with yampi. Muscle stretching exercises were prescribed for patients who showed soft tissue ankle equinus.

3.4.2.2.5. Monitoring

Leg pain observation diaries (Appendix VIII) were designed to monitor the effect of mechanical therapy on episodes of sleep disturbance and intolerance to physical exercise. Due to the poor response to these diaries, a simple "response to treatment" feedback form (Appendix VI) was designed and distributed to all patients.

Chapter 4

Results

4.1. Results of the questionnaire survey

4.1.1. Introduction

Following description of the patient and the Gp samples (section 4.1.2), data are presented in 3 sections covering the 3 main features under investigation namely, leg pain (section 4.1.3), sleep disturbance (section 4.1.4.) and intolerance to physical exercise (section 4.1.5). Under each section, the presentation of the results of the main feature and its subsequent analysis follow a similar pattern starting with a table showing the number of the various responses from the patient group, the Gp group or both. This is followed by a graph (figure) that illustrates the percentage of these responses. Finally, the details of the results of any applied statistical tests are presented.

4.1.2. Description of the samples

4.1.2.1. The patient sample

This sample comprised the respondents to the leg pain survey distributed to families of children with 22q11 deletion registered with the UK 22q11 support group. Out of 300 questionnaires sent out, 119 responses were received (Return rate 39.66%). The responses came from 53 females and 64 males (2 missing values). The age range is 2.8 to 17.8 years with a mean age of 8.95 (S.D. 3.83).

4.1.2.2. The general population (Gp) sample

This sample comprised the respondents to the leg pain survey distributed to children in 7 schools in Northamptonshire and 2 Schools in Sunderland, UK.

Out of 4507 questionnaires sent out, 1391 responses were received (Return rate 30.86%). 134 responses were disqualified due to age irregularities (absent date of birth or age over 20 years). Further 10 responses were disqualified due to one questionnaire being used to give details of more than one respondent. In all, 144 responses were disqualified and subsequent data analysis includes 1247 valid responses. The valid responses came from 616 females and 607 males (24 missing values). The age range is 3.4 to 19.7 years with a mean age of 10.16 (S.D 3.26).

4.1.2.3. Comparing the samples

Chi square test revealed that the patient and the Gp samples are gender matched with no significant difference in gender distribution between the two samples (χ^2 = 1.097, p = 0.295). Chi square test revealed however that there is a significant difference in the age distribution between the two samples (χ^2 = 49.247, p = 0.000). The patient and the Gp groups are therefore not age matched. The cases were therefore divided into 7 age groups and subsequent statistical analysis of each variable is performed within each individual age group so that the applied statistical tests can take account of the difference of age distribution between the patient and the Gp group.

4.1.3. Leg pain

4.1.3.1. Introduction

Section 4.1.3.2 presents the number and shows the percentage of patients and Gp subjects who reported leg pain. Cases of pain due to a known aetiology were than excluded in order to examine only cases that reported leg pain due to an unknown aetiology (PUA).

Section 4.1.3.3 examines the peak age and age distribution differences between the patient and the Gp groups. Originally 7 age groups were examined and these are presented as graphs (figures). Low frequencies in some age groups however rendered the data unsuitable for statistical analysis. The originally narrower 7 age groups were therefore amalgamated into 3 wider age categories with frequencies suitable for statistical analysis.

Section 4.1.3.4 examines gender prevalence differences within the patient and the Gp groups and section 4.1.3.5 compares the most common sites of lower limb pain in the patient and the Gp groups.

Analysis of reports of leg pain follows in sections 4.1.3.6 to 4.1.3.9, demonstrating the differences between the patient and the Gp groups in frequency, timing, duration and severity of leg pain episodes.

4.1.3.2 Reports of leg pain

Table 4.1.1 shows the number of subjects who reported leg pain in the patient and the Gp groups.

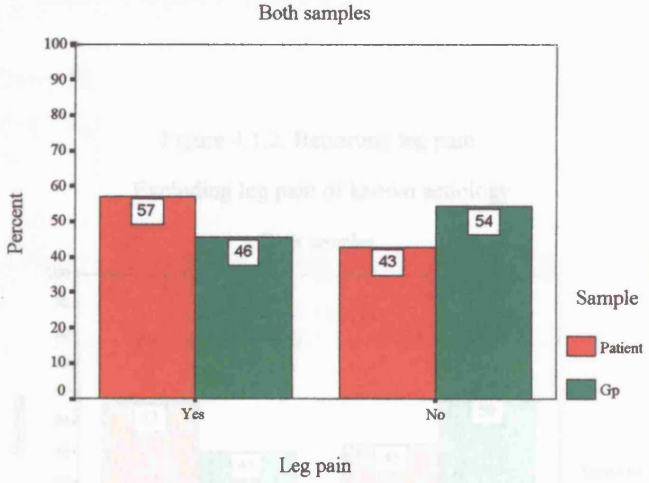
Table 4.1.1: Reports of leg pain

Both samples

	Pain	No pain	Total
Patients	**68**	**51**	**119**
Gp	**569**	**678**	**1247**
Total	**637**	**729**	**1366**

Figure 4.1.1 shows that 57% of patients reported leg pain compared to 46% of Gp subjects.

Figure 4.1.1: Reporting leg pain



Chi squared test applied to both groups revealed that there is a significant difference in the prevalence of complaint of leg pain between the patient and the Gp group ($\chi^2 = 5.786$, $p = 0.016$).

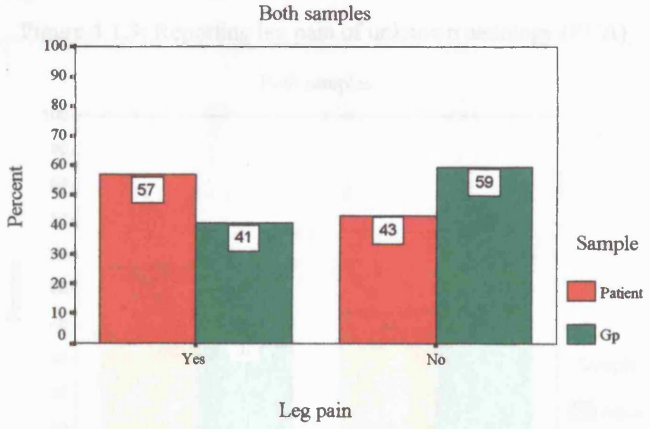
Table 4.1.2 shows the number of subjects who reported leg pain in the patient and the Gp group after excluding cases of pain due to a known aetiology e.g. Osgood-Schlatter disease, Chondromalacia Patellae, Tendonitis, Accidental or surgical trauma.

Table 4.1.2: Reports of leg pain
Excluding pain due to a known aetiology
Both samples

	Pain	No pain	Total
Patients	**67**	**51**	**118**
Gp	**464**	**678**	**1142**
Total	**531**	**729**	**1260**

Figure 4.1.2 shows that the effect of excluding cases of pain due to a known aetiology is greater in the Gp group, with a 5% reduction in the prevalence of leg pain reporting.

Figure 4.1.2: Reporting leg pain
Excluding leg pain of known aetiology



Exclusion of cases of leg pain due to a known aetiology, increased the level of the significance of the difference to $p = 0.001$ ($\chi^2 = 11.439$).

The term "Pain of an unknown aetiology (PUA)" is used to denote a complaint of leg pain of an unknown aetiology. The term "Other" is used to denote an absence of a complaint of leg pain or a complaint of leg pain due to a known aetiology.

Table 4.1.3 shows the number of subjects who reported leg pain in the patient and the Gp group after adding cases of pain due to a known aetiology to the category of "Other".

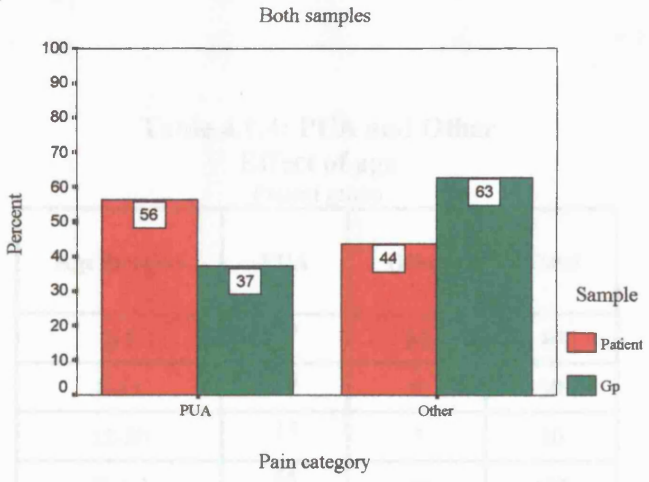
Table 4.1.3: Reports of leg pain
PUA and other
Both samples

	PUA	Other	Total
Patients	67	52	119
Gp	461	779	1240
Total	528	831	1359

PUA = Pain of an unknown aetiology
Other = No pain or pain due to a known aetiology

Figure 4.1.3 shows the effect of adding cases of pain due to a known aetiology to the category of "Other".

Figure 4.1.3: Reporting leg pain of unknown aetiology (PUA)



This further refining of the data by adding the cases of pain due to a known aetiology to the category of "Other", further increased the level of significance of the difference to $p = 0.000$ ($\chi^2 = 16.717$).

A complaint of leg pain of an unknown aetiology therefore, appears to be significantly more prevalent in children with 22q11 deletion than children of the general population.

Prevalence of leg pain of unknown aetiology

Frequency analysis showed that 67 out of 119 subjects in the patient group (56.3%) reported recurrent episodes of leg pain of unknown aetiology compared to only 461 out of 1240 subjects in the Gp group (37.2%).

All subsequent statistical analysis will only include two categories; cases that reported leg pain of an unknown aetiology (PUA) and cases that reported no leg pain and recurrent leg pain due to a known aetiology (Other).

4.1.3.3. Effect of age

Table 4.1.4 shows the number of subjects who reported PUA and "Other" in the various age categories in the patient group. The age categories are combined to avoid low frequencies in some age categories, which would render Chi squared test invalid.

Table 4.1.4: PUA and Other
Effect of age
Patient group

Age in years	PUA	Other	Total
2-7	19	26	45
8-11	30	9	39
12-20	13	7	20
Total	65	42	107

PUA = Pain of an unknown aetiology
Other = No pain or pain due to a known aetiology

Figure 4.1.4 shows the distribution of PUA across the various age categories of the patient group, highlighting the percentage of reports of PUA from each age category.

Figure 4.1.4: Distribution of age categories across pain types

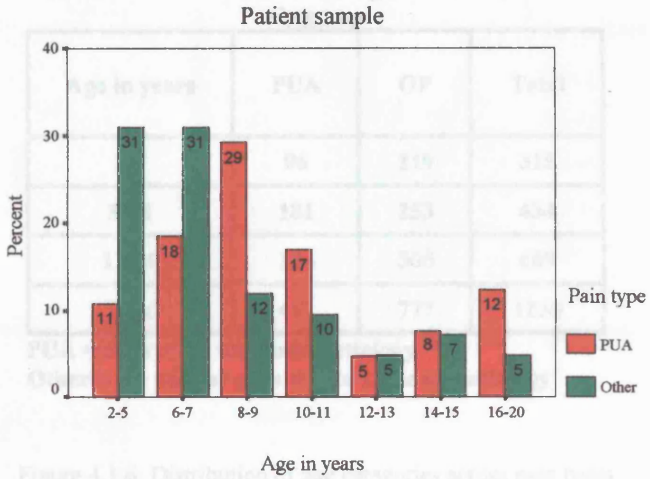
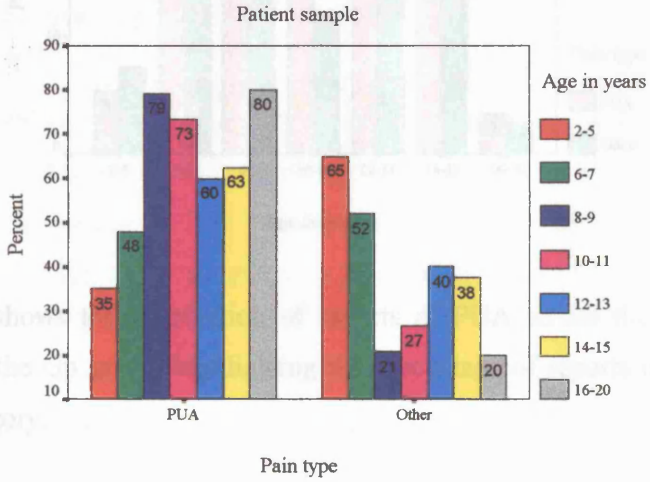


Figure 4.1.5 shows the distribution of patients who reported PUA in each age category, highlighting the percentage of reports of PUA within each age category.

Figure 4.1.5: PUA in each age category



A Chi squared test applied to the patient group only revealed that significantly more patients between the ages of 8 and 11 years reported leg pain of unknown aetiology than children between the age of 2 and 7 years (χ^2 =10.351, p = 0.001).

Table 4.1.5 shows the number of subjects who reported PUA and "Other" in the various age categories in the Gp group. The age categories are combined to allow comparison with the patient group.

Table 4.1.5: PUA and Other
Effect of age
Gp group

Age in years	PUA	OP	Total
2-7	96	219	315
8-11	181	253	434
12-20	184	305	489
Total	461	777	1238

PUA = Pain of an unknown aetiology
Other = No pain or pain due to a known aetiology

Figure 4.1.6: Distribution of age categories across pain types

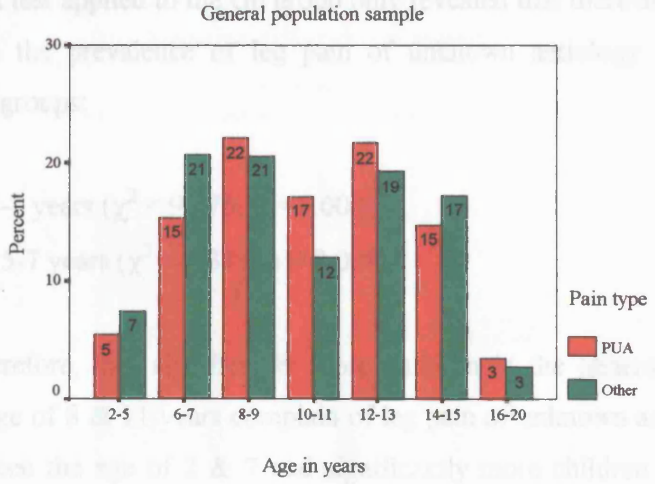
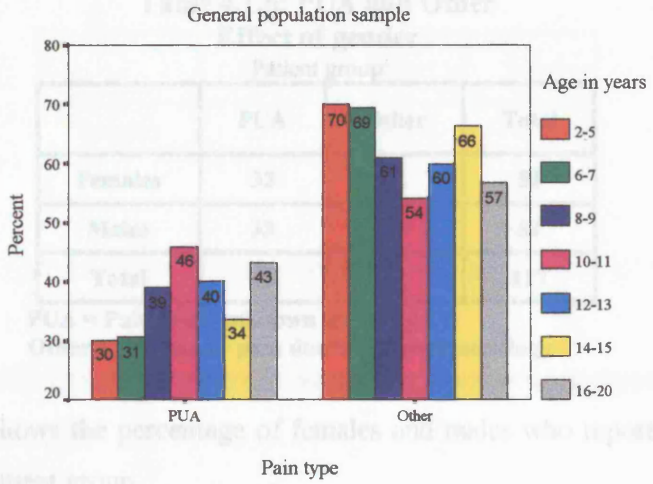


Figure 4.1.6 shows the distribution of reports of PUA across the various age categories of the Gp group, highlighting the percentage of reports of PUA from each age category.

Figure 4.1.7 shows the distribution of Gp subjects who reported PUA in each age category, highlighting the percentage of reports of PUA within each age category.

Figure 4.1.7: PUA in each age category



A Chi squared test applied to the Gp group only revealed that there are significant differences in the prevalence of leg pain of unknown aetiology between the following age groups:

8-11 years > 2-7 years ($\chi^2 = 9.875$, $p = 0.002$)

12-20 years > 5-7 years ($\chi^2 = 4.317$, $p = 0.038$)

It appears therefore, that significantly more children in the general population between the age of 8 & 11 years complain of leg pain of unknown aetiology than children between the age of 2 & 7 and significantly more children between the age of 12 & 20 years complain of leg pain of unknown aetiology than children between the age of 2 & 7 years.

Chi squared test applied to both groups showed that significantly more patients reported PUA than Gp subjects in all age groups:

2-7: ($\chi^2 = 21.445$, $p = 0.000$).

8-11: ($\chi^2 = 17.962$, $p = 0.000$).

12-20: ($\chi^2 = 6.068$, $p = 0.014$).

4.1.3.4. Effect of gender

Table 4.1.6 shows the number of subjects of each gender within the patient group, who reported PUA and Other.

Table 4.1.6: PUA and Other
Effect of gender

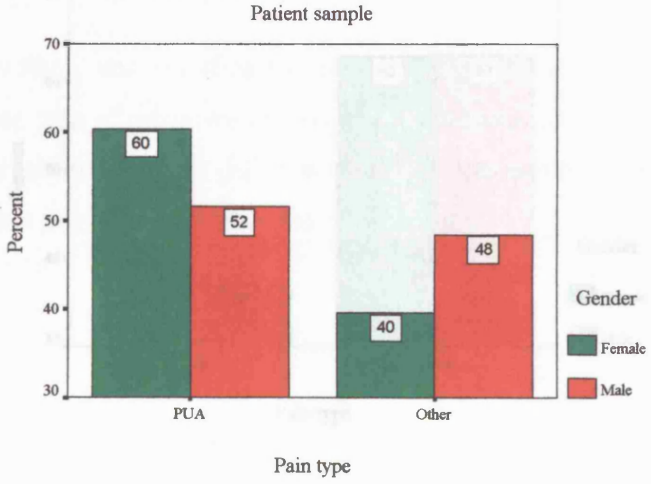
Patient group

	PUA	Other	Total
Females	32	21	53
Males	33	31	64
Total	65	52	117

PUA = Pain of an unknown aetiology.
Other = No pain or pain due to a known aetiology

Figure 4.1.8 shows the percentage of females and males who reported PUA and Other in the patient group.

Figure 4.1.8: PUA in both genders



Chi squared test applied to the patient group only showed no significant difference in the prevalence of PUA between females and males ($\chi^2 = 0.912$, p = 0.339).

Table 4.1.7 shows the number of subjects of each gender within the Gp group, who reported PUA and Other.

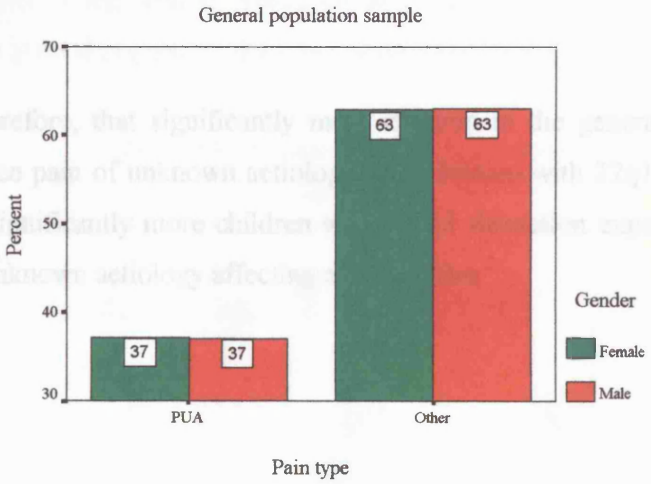
Table 4.1.7: PUA and Other
Effect of gender
Gp group

	PUA	Other	Total
Females	227	384	611
Males	224	381	605
Total	451	765	1216

PUA = Pain of an unknown aetiology.
Other = No pain or pain due to a known aetiology

Figure 4.1.9 shows the percentage of females and males who reported PUA and Other in the Gp group.

Figure 4.1.9: PUA in both genders



Chi squared test applied to the Gp group only showed no significant difference in the prevalence of PUA between females and males of the Gp group ($\chi^2 = 0.002$, p = 0.963).

4.1.3.5. Site of pain

Chi squared tests were applied to both groups and only cases of PUA were considered. The analysis looked for significant difference between the two groups for each site within the lower limb. The following sites showed significant difference between the two groups:

Knee pain: Gp group > Patient group ($\chi^2 = 8.257$, $p = 0.004$).

Foot pain: Patient group > Gp group ($\chi^2 = 30.189$, $p = 0.000$).

Ankle pain: Patient group > Gp group ($\chi^2 = 7.278$, $p = 0.007$).

Below knee pain: Patient group > Gp group ($\chi^2 = 16.871$, $p = 0.000$).

Pain in the back of the limb: Patient group > Gp group ($\chi^2 = 17.962$, $p = 0.000$).

Front foot pain: Patient group > Gp group ($\chi^2 = 26.228$, $p = 0.000$).

Back foot pain: Patient group > Gp group ($\chi^2 = 20.237$, $p = 0.000$).

Pain in the back of the ankle: Patient Group > Gp group ($\chi^2 = 7.346$, $p = 0.025$).

Pain below the back of the knee: Patient group > Gp group ($\chi^2 = 22.595$, $p = 0.000$).

It appears therefore, that significantly more children in the general population experience knee pain of unknown aetiology than children with 22q11 deletetion. By contrast, significantly more children with 22q11 deletetion experience lower limb pain of unknown aetiology affecting all other sites.

4.1.3.6. Frequency of leg pain episodes

Table 4.1.8 shows the distribution of responses from members of each group across the various "Frequency of leg pain episodes" categories.

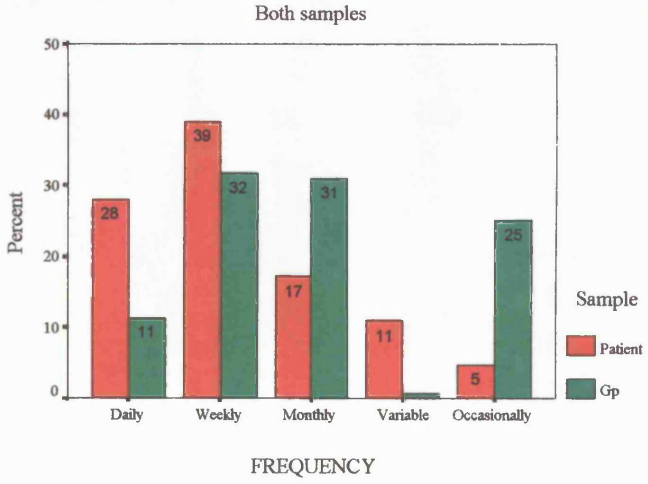
Table 4.1.8: The frequency of leg pain episodes

Both groups

Frequency	Group	
	Patient	Gp
Daily	18	50
Weekly	25	140
Monthly	11	137
Variable	7	3
Occasionally	3	111
Total	64	441

Figure 4.1.10 shows that proportionately more patients experience daily and weekly episodes of leg pain of unknown aetiology while similar episodes in children of the general population are more likely to be monthly or occasionally.

Figure 4.1.10: Frequency of leg pain episodes



Chi squared tests applied to both groups showed a significant difference in the frequency of leg pain episodes between the two groups in the following categories:

Daily episodes are significantly more common in patients than Gp subjects (χ^2 = 13.517, p = 0.000).

Variable frequency is significantly more common in patients than Gp subjects (χ^2 = 30.295, p = 0.000).

Monthly episodes are significantly more common in Gp subjects than in patients (χ^2 = 5.196, p = 0.023).

Occasional episodes are significantly more common in Gp subjects than in patients (χ^2 = 5.165, p = 0.023).

It appears therefore, that children with 22q11 deletion experience more frequent episodes of leg pain of unknown aetiology than children of the general population. It also appears that a variable pattern of frequency is more common in children with 22q11 deletion than in children in the general population.

4.1.3.7. Time of leg pain episodes

Table 4.1.9 shows the distribution of responses from members of each group across the various "Time of leg pain episodes" categories

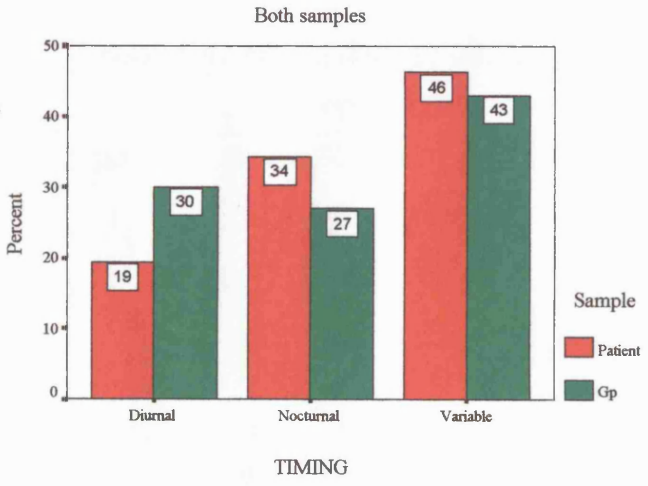
Table 4.1.9: Time of leg pain episodes

Both groups

Time	Group	
	Patient	Gp
Day	13	138
Night	23	124
Variable	31	198
Total	67	460

Figure 4.1.11 shows that proportionately more children with 22q11 deletion experience night and variable night and day episodes of leg pain of unknown aetiology while proportionately more children of the general population experience daytime episodes of leg pain.

Figure 4.1.11: Time of leg pain episodes



Chi squared test applied to the patient group only showed that significantly more patients experience variable circadian episodes of PUA than those who experience diurnal episodes of PUA ($\chi^2 = 10.964$, $p = 0.001$).

Chi squared test applied to the Gp group only showed that significantly more Gp subjects experience variable episodes than diurnal (χ^2 = 16.879, p = 0.000) and nocturnal (χ^2 = 26.163, p = 0.000) episodes of PUA.

Chi squared test applied to both groups showed no significant difference between the two groups, in diurnal episodes (χ^2 = 3.213, p = 0.073), nocturnal episodes (χ^2 = 1.580, p = 0.209) or variable cercadian episodes (X^2 = 0.248, p = 0.619).

4.1.3.8. Duration of each leg pain episode

Table 4.1.10 shows the distribution of responses from members of each group across the various "Duration of leg pain episodes" categories.

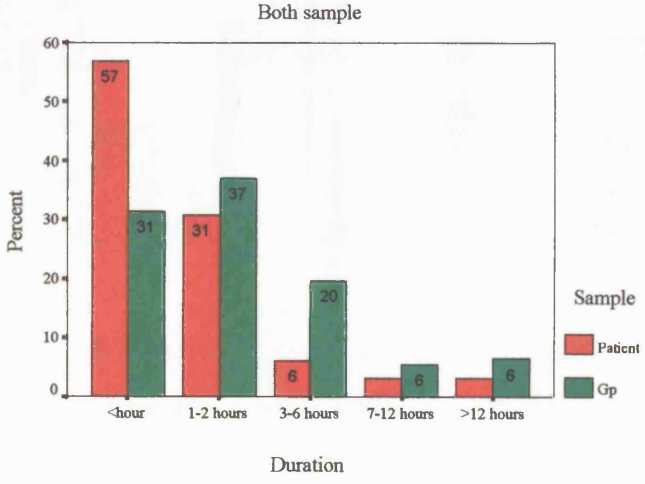
Table 4.1.10: Duration of leg pain episodes

Both groups

Duration	Group	
	Patient	Gp
< 1 hour	37	142
1-2 hours	20	168
3-6 hours	4	89
7-12hours	2	25
> 12 hours	2	29
Total	65	453

Figure 4.1.12 shows that proportionately more patients experience episodes of PUA lasting less than one hour at a time than Gp subjects, while proportionately more Gp subjects experience episodes of PUA of longer duration.

Figure 4.1.12: Duration of leg pain episodes



Chi squared test applied to both groups showed that significantly more patients experienced leg pain episodes lasting for less than one hour at a time than Gp subjects (χ^2 = 16.443, p = 0.000), while significantly more Gp subjects experienced leg pain episodes lasting 3-6 hours at a time than patients (χ^2 = 7.026, p = 0.008).

It appears therefore, that episodes of leg pain of unknown aetiology are shorter in duration in children with 22q11 deletion than children of the general population.

4.1.3.9. Severity of leg pain episodes

Table 4.1.11 shows the distribution of responses from members of each group across the various "Severity of leg pain episodes" categories.

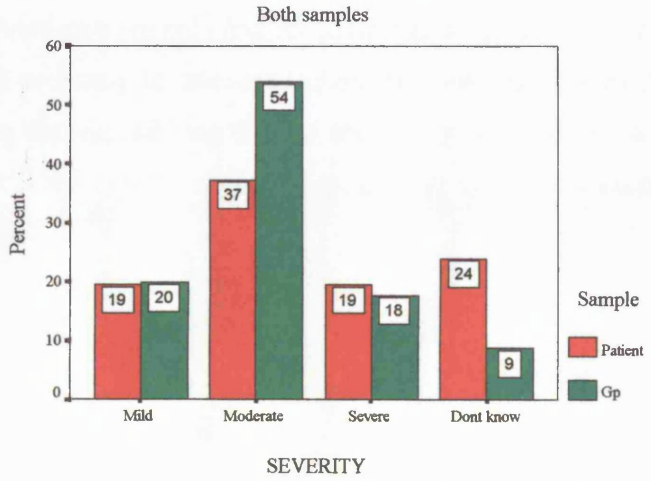
Table 4.1.11: Severity of leg pain episodes

Both groups

Severity	Group	
	Patient	Gp
Mild	13	91
Moderate	25	248
Severe	13	81
Don't know	16	40
Total	67	460

Figure 4.1.13 shows that proportionately more Gp subjects described their leg pain episodes as moderate in severity while proportionately more patients were unable to rate the severity of their pain episodes.

Figur 4.1.13: Severity of leg pain episodes



Chi squared test applied to both groups showed that significantly more Gp subjects reported moderate pain than patients (χ^2 = 6.454, p = 0.011) while significantly more patients than Gp subjects were not able to rate the severity of their pain episodes (χ^2 = 14.199, p = 0.000). It appears therefore, that significantly more children with 22q11 deletion are unable to describe their leg pain in terms of severity.

4.1.3.10. Summary

- Significantly more patients with 22q11 deletion report PUA than children and adolescents of the general population (Gp).
- The peak age for PUA in patients with 22q11 deletion is 8-9 years old.
- The age distribution for PUA in the Gp follows a biphasic pattern peaking at the ages of 8-9 and 12-13 years old.
- There is equal gender prevalence for PUA in both populations.
- The most common site of PUA in patients is the calf muscle area whereas the knee is the most common site in the Gp.
- Episodes of PUA recur more frequently in patients than in the Gp.
- Episodes of PUA occur during the day or the night in both populations.
- Episodes of PUA are shorter in duration in patients than in the Gp.
- Episodes of PUA are most commonly perceived as moderate in severity in both populations.
- Significantly more patients were not able to describe the severity of their PUA than subjects of the Gp.

4.1.4. Sleep disturbance

4.1.4.1 Introduction

Section 4.1.4.2. presents the number and shows the percentage of patients and Gp subjects who reported sleep disturbance. Section 4.1.4.3 examines the peak age and age distribution differences between the patient and the Gp groups. Similar to age analysis of PUA (section 4.1.3.3) originally 7 age groups were examined and these are presented as graphs (figures). Low frequencies in some age groups however rendered the data unsuitable for statistical analysis. The originally narrower 7 age groups were therefore amalgamated into 3 wider age categories with frequencies suitable for statistical analysis.

Section 4.1.4.4 examines gender prevalence differences between the patient and the Gp groups. Analysis of reports of sleep disturbance follows in sections 4.1.4.5 to 4.1.4.12 The reason behind the data presented in sections 4.1.4.6 to 4.1.4.12 stems from two arguable possibilities. The possibility that sleep disturbance may be due to leg pain and the possibility that children with 22q11 deletion may experience leg pain and for some reason do not verbally express it. It was therefore necessary to examine features that may suggest leg pain. These included kicking the legs, rubbing the legs and crying. Comparing the prevalence of such features in the patient and the Gp groups may or may not suggest either or both possibilities.

4.1.4.2. Reports of sleep disturbance

Table 4.1.12 shows the number of subjects who reported sleep disturbance in both groups.

Table 4.1.12: Sleep disturbance

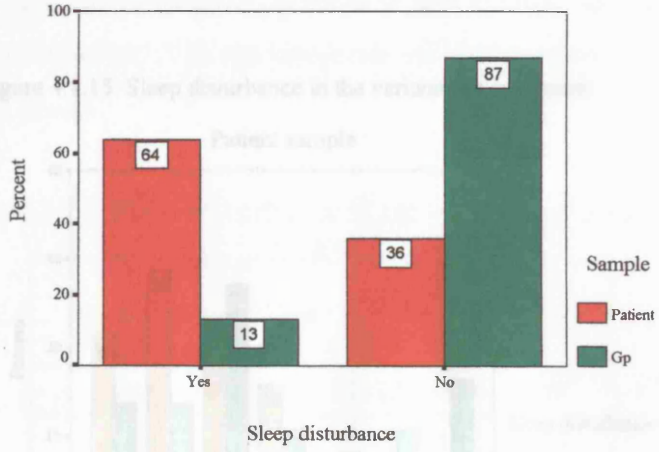
Both groups

	Yes	No	Total
Patients	**76**	**43**	**119**
Gp	**164**	**1076**	**1240**
Total	**240**	**1119**	**1359**

Figure 4.1.14 shows that proportionately more patients report sleep disturbance than Gp subjects.

Figure 4.1.14: Sleep disturbance

Both samples



Chi squared test applied to both groups revealed that significantly more patients experience sleep disturbance than Gp subjects ($\chi^2 = 200.289$, $p = 0.000$).

Sleep disturbance therefore, appears to be significantly more prevalent in children with 22q11 deletion than children of the general population.

4.1.4.3. Effect of age

Table 4.1.13. shows the number of patients who reported sleep disturbance in the various age categories. The age categories are combined to avoid the low frequencies in some age categories, which would render Chi squared test invalid.

Table 4.1.13: Sleep disturbance in the various age categories

Patient group

Age in years	Yes	No	Total
2-7	35	10	45
8-9	25	14	39
12-20	10	13	23
Total	70	37	107

Figure 4.1.15 shows the distribution of reports of sleep disturbance across the various age categories of the patient group, highlighting the percentage of members of each age category who reported sleep disturbance.

Figure 4.1.15: Sleep disturbance in the various age categories

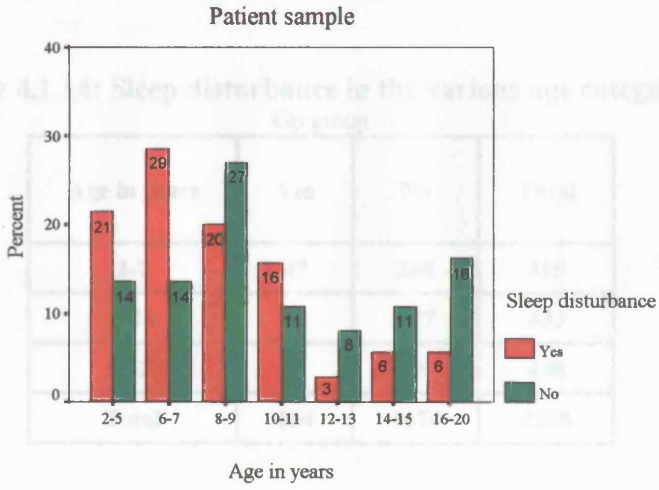


Figure 4.1.16 shows the distribution of patients who reported sleep disturbance in each age category, highlighting the percentage of reports of sleep disturbance within each age category.

Figure 4.1.16: Sleep disturbance in each age category

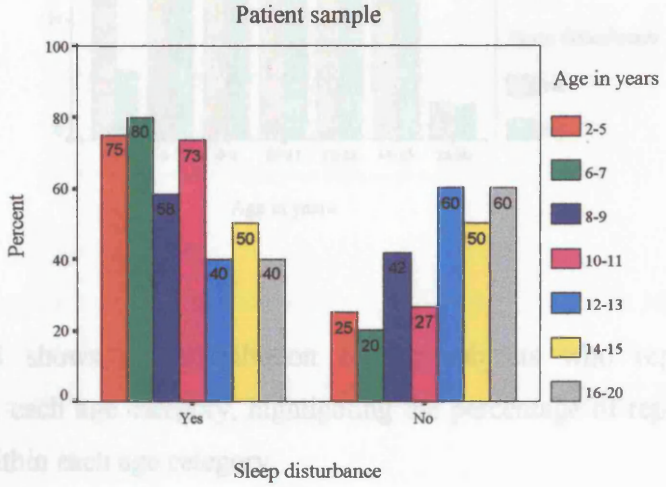


Table 4.1.14. shows the number of Gp subjects who reported sleep disturbance in the various age categories. The age categories are combined to allow comparison with the patient group.

Table 4.1.14: Sleep disturbance in the various age categories

Gp group

Age in years	Yes	No	Total
2-7	47	268	315
8-11	56	377	433
12-20	61	429	490
Total	164	1074	1238

Figure 4.1.17 shows the distribution of reports of sleep disturbance across the various age categories of the Gp group, highlighting the percentage of members of each age group who reported sleep disturbance.

Figure 4.1.17: Sleep disturbance in the various age categories

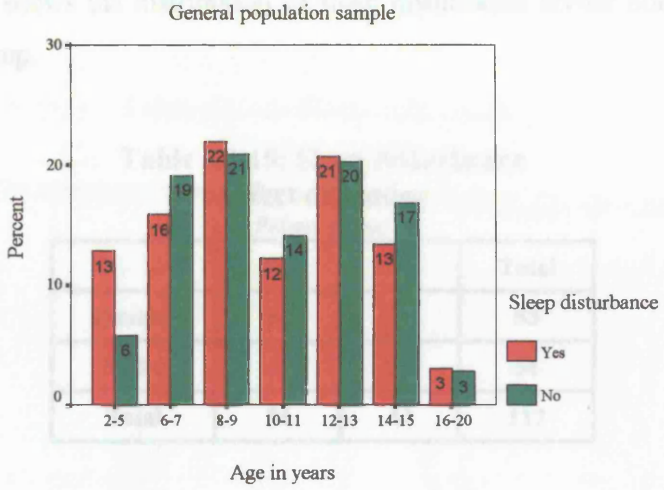
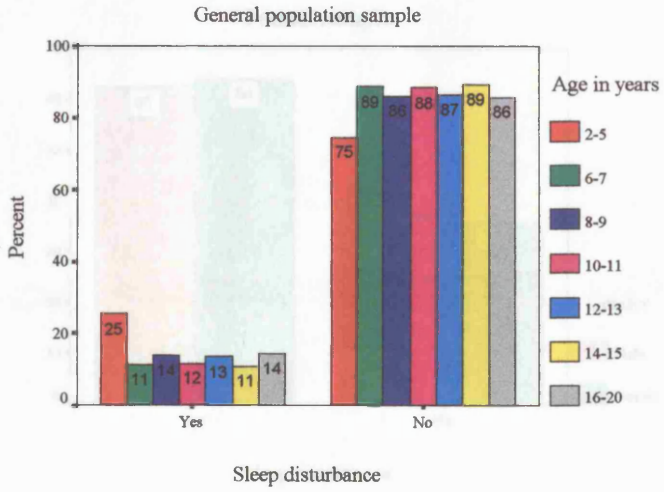


Figure 4.1.18 shows the distribution of Gp subjects who reported sleep disturbance in each age category, highlighting the percentage of reports of sleep disturbance within each age category.

Figure 4.1.18: Sleep disturbance in the each age category



Chi squared test applied to both groups revealed that significantly more patients than Gp subjects reported sleep disturbance in all age categories ($p = 0.000$).

4.1.4.4. Effect of gender

Table 4.1.15. shows the distribution of sleep disturbance across both genders in the patient group.

Table 4.1.15: Sleep disturbance
Effect of gender
Patient group

	Yes	No	Total
Females	**34**	**19**	**53**
Males	**40**	**24**	**64**
Total	**74**	**43**	**117**

Figure 4.1.19 shows that proportionately slightly more females reported sleep disturbance than males within the patient group. However, Chi squared test applied to the patient group only showed that this was not statistically significant ($\chi^2 = 0.034$, $P = 0.854$).

Figure 4.1.19: Sleep disturbance in both genders

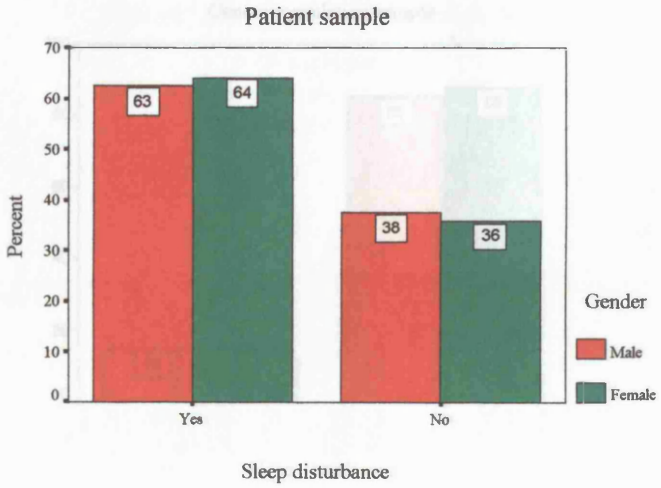


Table 4.1.16. shows the distribution of sleep disturbance across both genders in the Gp group.

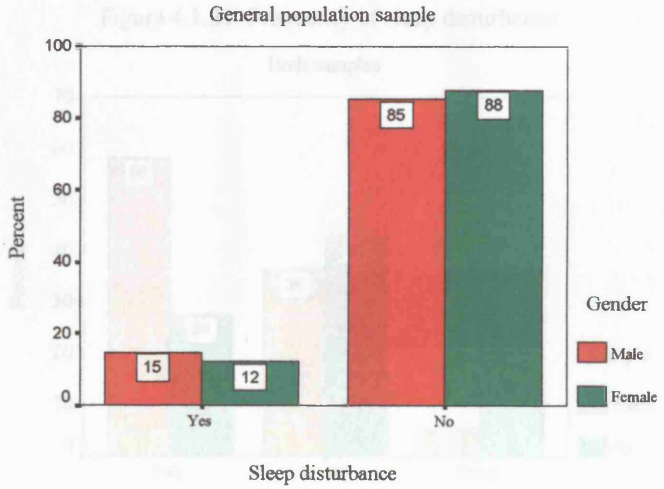
Table 4.1.16: Sleep disturbance
Effect of gender

Gp group

	Yes	No	Total
Females	**74**	**537**	**611**
Males	**89**	**516**	**605**
Total	**163**	**1053**	**1216**

Figure 4.1.20 shows that proportionately slightly more males suffer excessive sleep disturbance than females within the Gp group. However, Chi squared test applied to the Gp group only showed that this was not statistically significant ($\chi^2 = 1.770$, $p = 0.183$).

Figure 4.1.20: Sleep disturbance in both genders



4.1.4.5. Frequency of episodes of sleep disturbance

Table 4.1.17. shows the distribution of members of each group across the various "Frequency of episodes of sleep disturbance" categories. The category "Others" was created to combine categories with small number of responses including monthly, occasionally, variable and don't know.

Table 4.1.17: The frequency of episodes of sleep disturbance

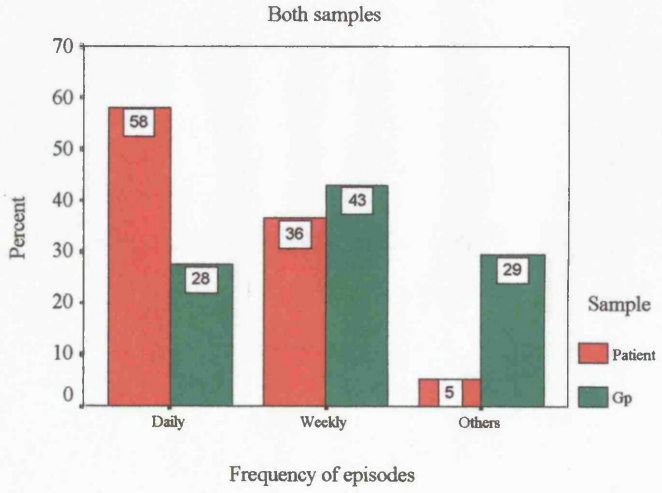
Both groups

Frequency	Group	
	Patient	Gp
Daily	43	43
Weekly	27	67
Others	4	46
Total	74	156

Others = Monthly, Occasionally, Variable and Don't know

Figure 4.1.21 shows that proportionately more patients reported daily episodes of sleep disturbance while more Gp subjects reported weekly and other frequency of episodes of sleep disturbance.

Figure 4.1.21: Frequency of sleep disturbance



Chi squared test applied to both groups showed that significantly more patients reported daily episodes of sleep disturbance than Gp subjects ($\chi^2 = 20.002$, $p = 0.000$) and significantly more Gp subjects reported other frequencies of episodes of sleep disturbance than patients, including monthly, occasionally, variable and don't know ($\chi^2 = 17.109$, $p = 0.002$).

It appears therefore, that children with 22q11 deletions experience more frequent episodes of sleep disturbance than children of the general population.

4.1.4.6. Sleep disturbance with reporting leg pain

Table 4.1.18. shows the number of patients and Gp subjects who reported leg pain during episodes of sleep disturbance.

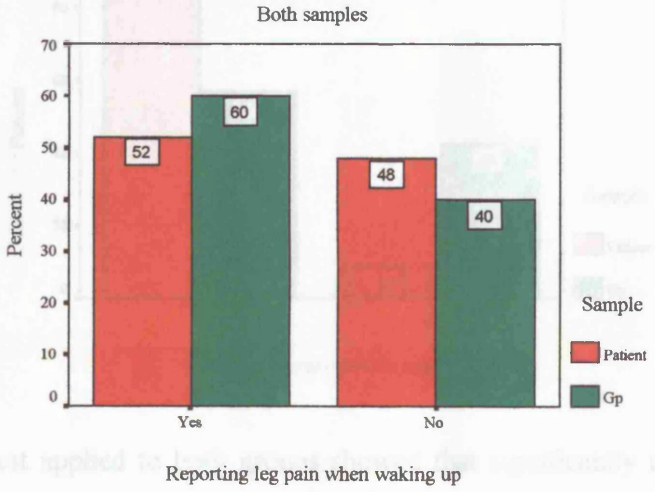
Table 4.1.18: Sleep disturbance Reporting leg pain

Both groups

	Yes	No	Total
Patients	**37**	**34**	**71**
Gp	**87**	**58**	**145**
Total	**124**	**92**	**216**

Figure 4.1.22 shows that proportionately more Gp subjects woke up complaining of leg pain than patients. However, Chi squared test applied to both groups showed that this was not statistically significant ($\chi^2 = 1.213$, $p = 0.271$).

Figure 4.1.22: Sleep disturbance with leg pain



4.1.4.7. Sleep disturbance for no obvious reason

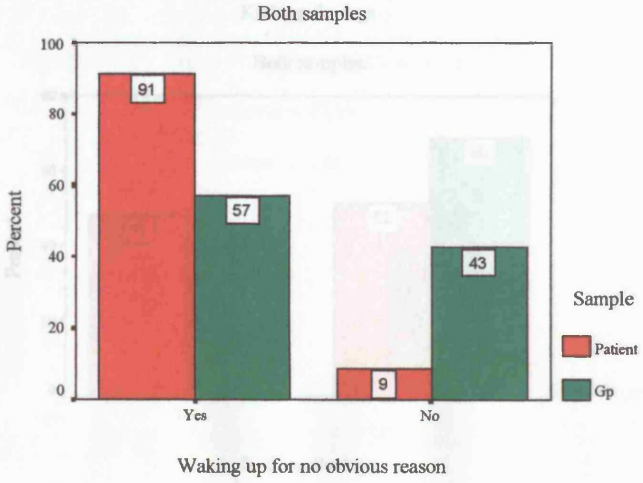
Table 4.1.19. shows the number of patients and Gp subjects who woke up for no obvious reason.

Table 4.1.19: Sleep disturbance
No obvious reason
Both groups

	Yes	No	Total
Patients	**64**	**6**	**70**
Gp	**71**	**53**	**124**
Total	**135**	**59**	**194**

Figure 4.1.23 shows that proportionately more patients woke up for no obvious reason than Gp subjects.

Figure 4.1.23: Sleep disturbance for no obvious reason



Chi squared test applied to both groups showed that significantly more patients woke up for no obvious reason than Gp subjects ($\chi^2 = 24.685$, $p = 0.000$).

4.1.4.8. Sleep disturbance with kicking the legs

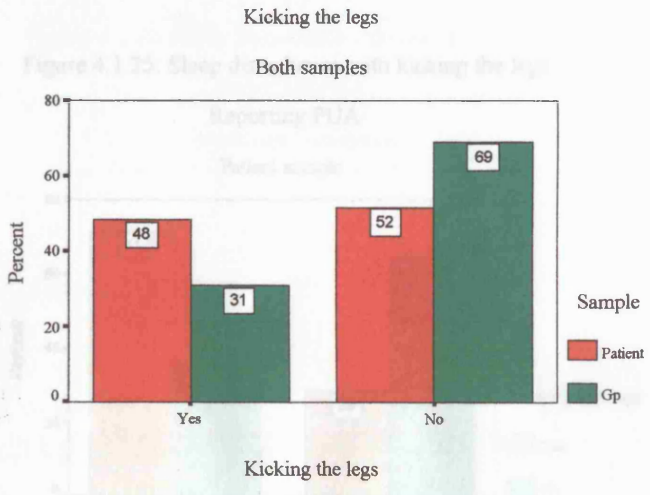
Table 4.1.20. shows the number of patients and Gp subjects who woke up kicking their legs.

Table 4.1.20: Sleep disturbance
Kicking the legs
Both groups

	Yes	No	Total
Patients	**29**	**31**	**60**
Gp	**36**	**80**	**116**
Total	**65**	**111**	**176**

Figure 4.1.24 shows that proportionately more patients woke up kicking their legs than Gp subjects.

Figure 4.1.24: Sleep disturbance



Chi squared test applied to both groups showed that significantly more patients woke up kicking their legs than Gp subjects ($\chi^2 = 5.081$, $p = 0.024$).

4.1.4.9. Sleep disturbance with kicking the legs and not reporting PUA

Table 4.1.21. shows the number of patients who woke up kicking their legs without reporting PUA.

Table 4.1.21: Sleep disturbance Reporting PUA and kicking the legs

Patient group

Kicking Leg pain	Yes	No	Total
Yes	20	10	30
No	8	18	26
Total	28	28	56

Figure 4.1.25 shows that 29% of patients who woke up kicking their legs, did not report leg pain during episodes of sleep disturbance.

Figure 4.1.25: Sleep disturbance with kicking the legs

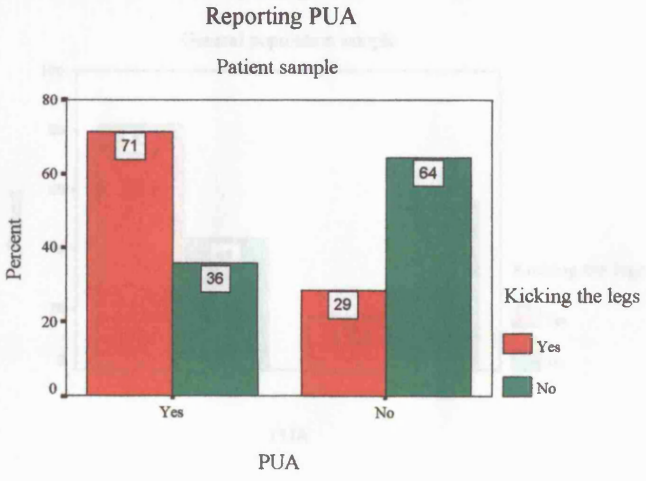


Table 4.1.22. shows the number of Gp group subjects who woke up kicking their legs without reporting PUA.

Table 4.1.22: Sleep disturbance
Reporting pain and kicking the legs

Gp group

Kicking / Leg pain	Yes	No	Total
Yes	27	34	61
No	6	44	50
Total	33	78	111

Figure 4.1.26 shows that 18% of the Gp subjects who woke up kicking their legs, did not report leg pain during episodes of sleep disturbance.

Figure 4.1.26: Sleep disturbance with kicking the legs

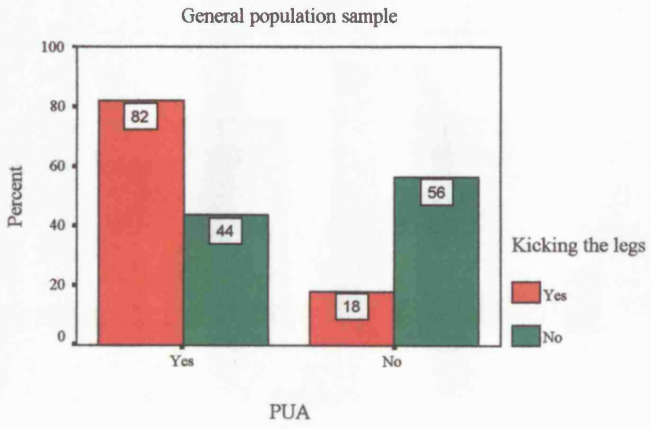


Table 4.1.23. shows the number of subjects of both groups who woke up kicking their legs with and without reporting leg pain, excluding cases of pain due to a known aetiology.

Table 4.1.23: Sleep disturbance
Kicking the legs with and without leg pain
Both groups

	Without	With	Total
Patients	**8**	**20**	**28**
Gp	**6**	**27**	**33**
Total	**14**	**47**	**61**

Chi square test applied to both groups showed no significant difference between the two groups in the prevalence of kicking the legs on waking up without reporting of leg pain ($\chi^2 = 0.925$, $p = 0.336$).

4.1.4.10. Sleep disturbance and rubbing the legs

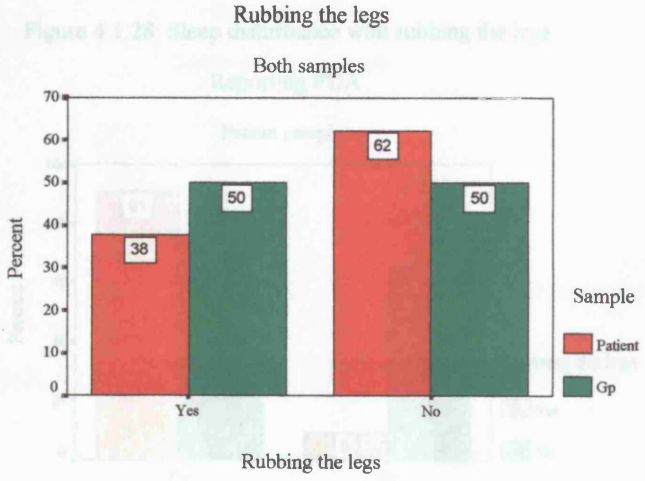
Table 4.1.24. shows the number of patients and Gp subjects who woke up rubbing their legs.

Table 4.1.24: Sleep disturbance
Rubbing the legs
Both groups

	Yes	No	Total
Patients	**23**	**38**	**61**
Gp	**63**	**63**	**126**
Total	**86**	**101**	**187**

Figure 4.1.27 shows that proportionately more Gp subjects woke up rubbing their legs than patients. However, Chi squared test applied to both groups showed that this was not statistically significant ($\chi^2 = 2.501$, $p = 0.114$).

Figure 4.1.27: Sleep disturbance



4.1.4.11. Sleep disturbance with rubbing the legs and not reporting PUA

Table 4.1.25. shows the number of patients who woke up rubbing their legs without reporting leg pain, excluding cases of pain due to a known aetiology.

Table 4.1.25: Sleep disturbance Reporting PUA and rubbing the legs

Patient group

Rubbing / Leg pain	Yes	No	Total
Yes	20	12	32
No	2	23	25
Total	22	18	57

Figure 4.1.28 shows that 9% of the patients who woke up rubbing their legs, did not report leg pain during episodes of sleep disturbance.

Figure 4.1.28: Sleep disturbance with rubbing the legs

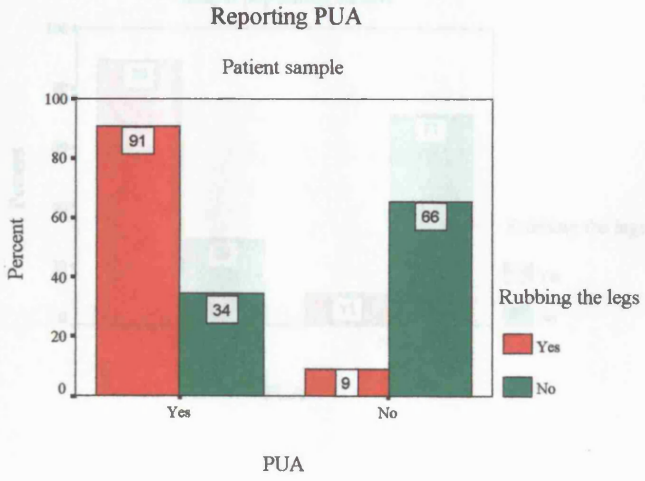


Table 4.1.26. shows the number Gp subjects who woke up rubbing their legs without reporting leg pain, excluding cases of pain due to a known aetiology.

Table 4.1.26: Sleep disturbance
Reporting leg pain and rubbing the legs

Gp group

Rubbing / Leg pain	Yes	No	Total
Yes	50	18	68
No	6	44	50
Total	56	62	118

Figure 4.1.29 shows that 11% of the Gp subjects who woke up rubbing their legs, did not report leg pain during episodes of sleep disturbance.

Figure 4.1.29: Sleep disturbance with rubbing the legs

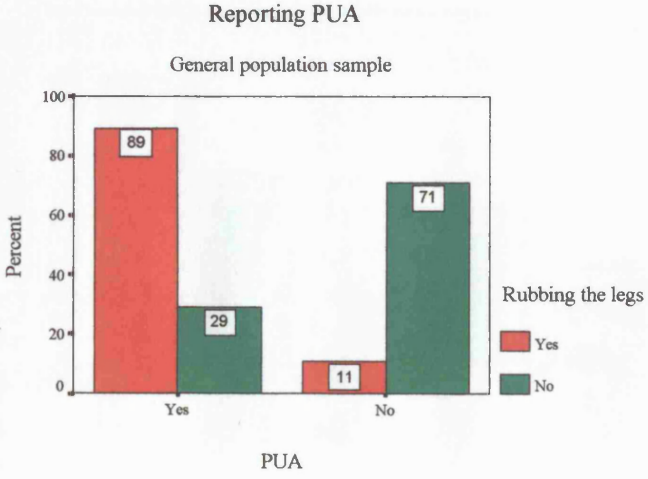


Table 4.1.27. shows the number of subjects of both groups who woke up rubbing their legs with and without reporting leg pain, excluding cases of pain due to a known aetiology.

Table 4.1.27: Sleep disturbance

Rubbing the legs with and without complaint

Both groups

	Without	With	Total
Patients	**2**	**20**	**22**
Gps	**6**	**50**	**56**
Total	**8**	**70**	**78**

Chi squared test applied to both groups showed no significant difference between the two groups in the prevalence of rubbing the legs on waking up without reporting leg pain ($\chi^2 = 0.045$, $p = 0.832$).

4.1.4.12. Sleep disturbance and crying

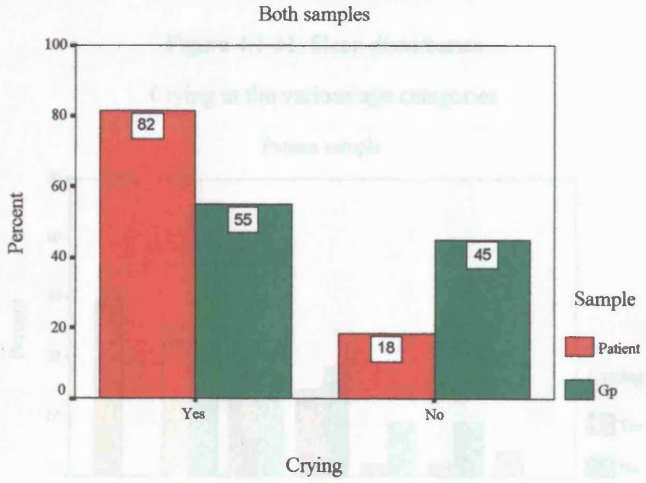
Table 4.1.28. shows the number of subjects of both groups who cried during episodes of sleep disturbance.

Table 4.1.28: Sleep disturbance
Crying
Both groups

	Crying	Not crying	Total
Patients	**53**	**12**	**65**
Gps	**72**	**59**	**131**
Total	**125**	**71**	**196**

Figure 4.1.30 shows that proportionately more patients woke up crying than Gp subjects.

Figure 4.1.30: Sleep disturbance with crying



Chi squared test applied to both groups showed that significantly more patients than Gp subjects cried during episodes of sleep disturbance (χ^2 = 13.282, p = 0.000).

Table 4.1.29. shows the number of patients who cried during episodes of sleep disturbance in the various age categories. The age categories are combined to account for the low frequency in some age categories, which would render Chi squared test invalid.

Table 4.1.29: Sleep disturbance
Crying in various age categories

Patient group

Crying / Age in years	Yes	No	Total
2-7	26	5	31
8-11	18	4	22
12-20	4	2	6
Total	48	11	59

Figure 4.1.31 shows the percentage of patients who cried during episodes of sleep disturbance in the various age categories.

Figure 4.1.31: Sleep disturbance

Crying in the various age categories

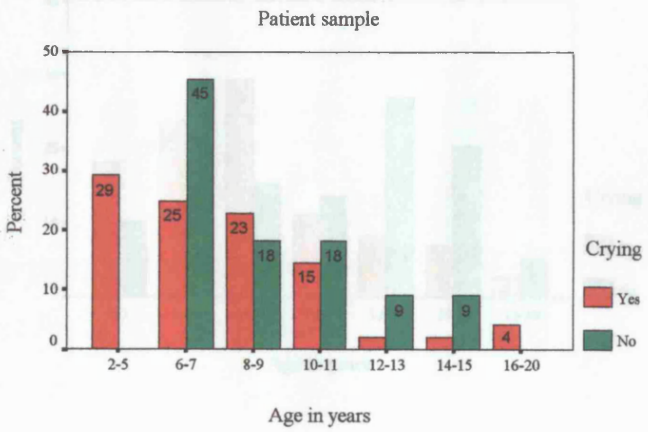


Table 4.1.30. shows the number of Gp subjects who cried during episodes of sleep disturbance in the various age categories.

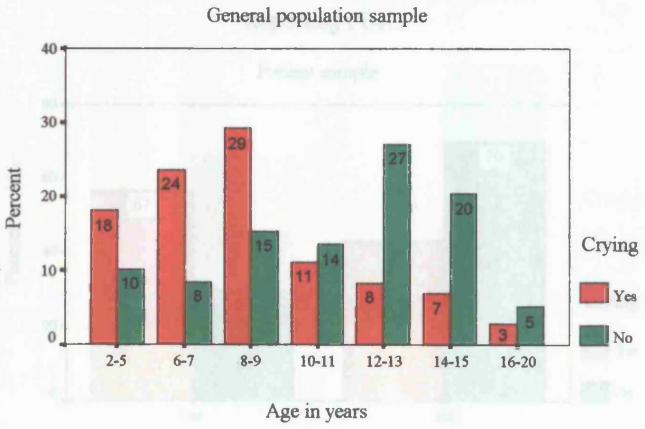
Table 4.1.30: Sleep disturbance
Crying in various age categories
Gp group

Crying / Age in years	Yes	No	Total
2-7	30	11	41
8-11	29	17	46
12-20	13	31	44
Total	72	59	131

Figure 4.1.32 shows the percentage of Gp subjects who cried during episodes of sleep disturbance in the various age categories.

Figure 4.1.32: Sleep disturbance

Crying in the various age categories



Chi squared test applied to both groups showed no significant difference between the patient and the Gp groups in the prevalence of waking up crying in all the age categories.

4.1.4.13. Sleep disturbance with crying and reporting PUA

Table 4.1.31. shows the number of patients who woke up crying without reporting PUA.

Table 4.1.31: Sleep disturbance Reporting leg pain and crying

Patient group

Crying / Leg pain	Yes	No	Total
Yes	29	3	32
No	22	7	29
Total	51	10	61

Figure 4.1.33 shows that 43% of the patients who woke crying, did not report PUA during episodes of sleep disturbance.

Figure 4.1.33: Sleep disturbance with crying

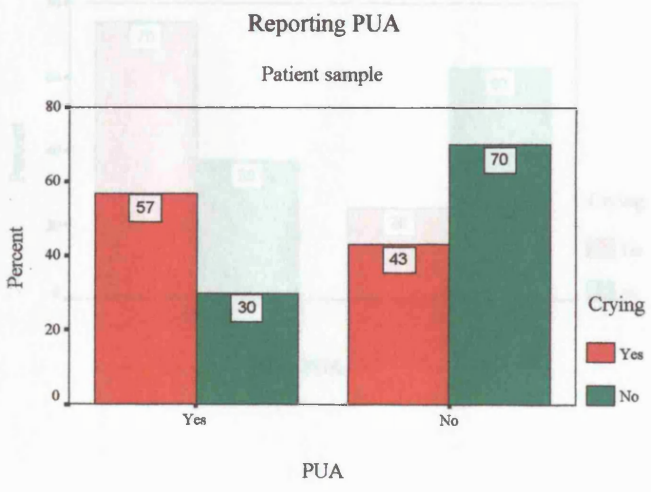


Table 4.1.32. shows the number of Gp subjects who woke up crying without reporting leg pain, excluding cases of pain due to a known aetiology.

Table 4.1.32: Sleep disturbance Reporting leg pain and crying

Gp group

Crying / Leg pain	Yes	No	Total
Yes	**48**	**21**	**69**
No	**16**	**35**	**51**
Total	**64**	**56**	**120**

Figure 4.1.34 shows that 25% of the Gp subjects who woke up crying, did not report leg pain during episodes of sleep disturbance.

Figure 4.1.34: Sleep disturbance with crying

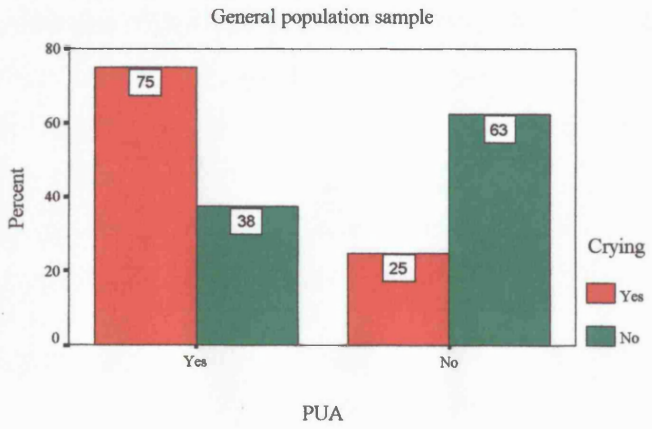


Table 4.1.33. shows the number of subjects of both groups who woke crying with and without a complaint of leg pain, excluding cases of pain due to a known aetiology.

Table 4.1.33: Sleep disturbance
Crying with and without leg pain
Both groups

	Without	With	Total
Patients	**22**	**29**	**51**
Gp	**16**	**48**	**64**
Total	**38**	**77**	**115**

Chi squared test applied to both groups showed that significantly more patients cried during episodes of sleep disturbance without reporting leg pain (χ^2 = 18.387, p = 0.000).

4.1.4.14. Summary

- Significantly more patients with 22q11 deletion report sleep disturbance than children and adolescents of the general population (Gp).
- The peak age for sleep disturbance in patients with 22q11 deletion is 6-7 years old.
- The age distribution for sleep disturbance in the Gp follows a biphasic pattern peaking at the ages of 8-9 and 12-13 years old.
- There is equal gender prevalence for sleep disturbance in both populations.
- Episodes of sleep disturbance recur more frequently in patients than in the Gp.
- Episodes of sleep disturbance for no obvious reason are more common in patients than in subjects of the Gp. occur during the day or the night in both populations.
- Data analysis does not support the notion that patients may not report an existing pain that may cause sleep disturbance.

4.1.5. Exercise intolerance

4.1.5.1. Introduction

Section 4.1.5.2. reports the number and shows the percentage of patients and Gp subjects who reported exercise intolerance. Section 4.1.5.3. examines the peak age and age distribution differences between the patient and Gp groups. Similar to age analysis of PUA (section 4.1.3.3.) and sleep disturbance (section 4.1.4.3) originally 7 age groups were examined and these are presented as graphs (figures). Low frequencies in some age groups however rendered the data unsuitable for statistical analysis. The originally narrower 7 age groups were therefore amalgamated into 3 wider age categories with frequencies suitable for statistical analysis.

Section 4.1.5.4. examines gender prevalence differences between the patient and the Gp groups. Analysis of reports of exercise intolerance follows in sections 4.1.5.5. to 4.1.5.11. The reason behind the data presented in sections 4.1.5.6. to 4.1.5.11. stems from two arguable possibilities. The possibility that exercise intolerance may be due to leg pain and the possibility that children with 22q11 deletion may experience leg pain and for some reason do not verbally express it. It was therefore necessary to examine features that may suggest leg pain. These included lagging behind during walking, demanding to be picked up during walking and crying. Comparing the prevalence of such features in the patient and the Gp groups may or may not suggest either or both possibilities.

4.1.5.2. Reports of exercise intolerance

Table 4.1.34. shows the number of subjects who reported exercise intolerance in both groups.

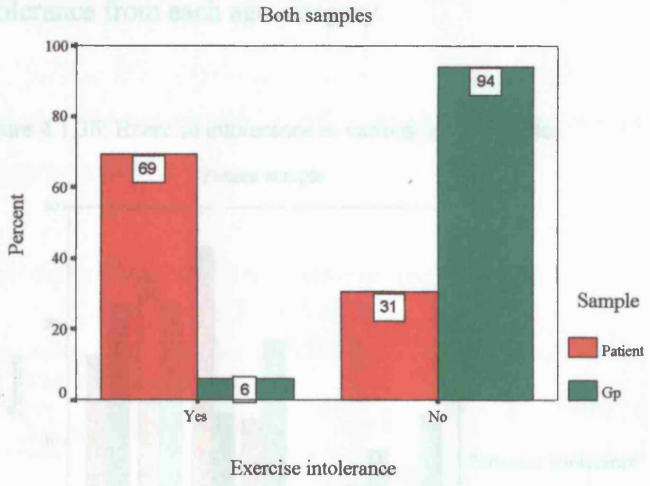
Table 4.1.34: Exercise intolerance

Both groups

	Yes	No	Total
Patients	**82**	**36**	**118**
Gps	**73**	**1169**	**1242**
Total	**155**	**1205**	**1360**

Figure 4.1.35 shows that proportionately more patients reported exercise intolerance than Gp subjects.

Figure 4.1.35: Exercise intolerance



Chi squared test applied to both groups revealed that a significantly more patients than Gp subjects reported exercise intolerance ($\chi^2 = 431.845$, $p = 0.000$)

4.1.5.3. Effect of age

Table 4.1.35. shows the number of patients who reported exercise intolerance in the various age categories.

Table 4.1.35: Exercise intolerance
Effect of age
Patient group

Exercise intolerance / Age in years	Yes	No	Total
2-7	31	14	45
8-11	29	10	39
12-20	15	8	23
Total	75	32	107

Figure 4.1.36 shows the distribution of reports of exercise intolerance across the various age categories of the patient group, highlighting the percentage of reports of exercise intolerance from each age category.

Figure 4.1.36: Exercise intolerance in various age categories

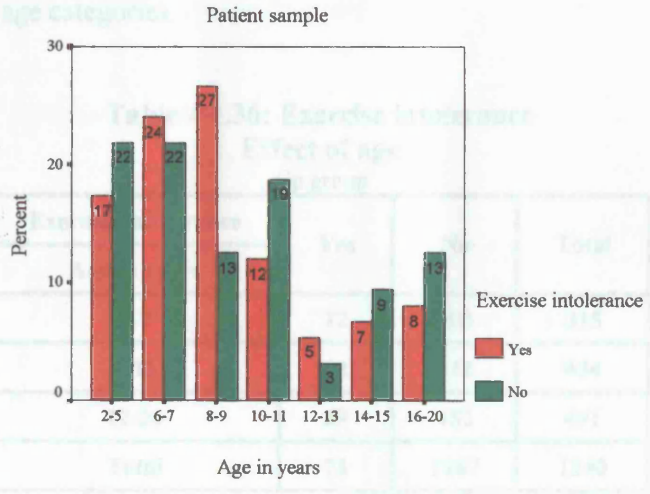


Figure 4.1.37 shows the distribution of patients who reported exercise intolerance in each age category, highlighting the percentage of reports of exercise intolerance within each age category.

Figure 4.1.37: Exercise intolerance in each age category

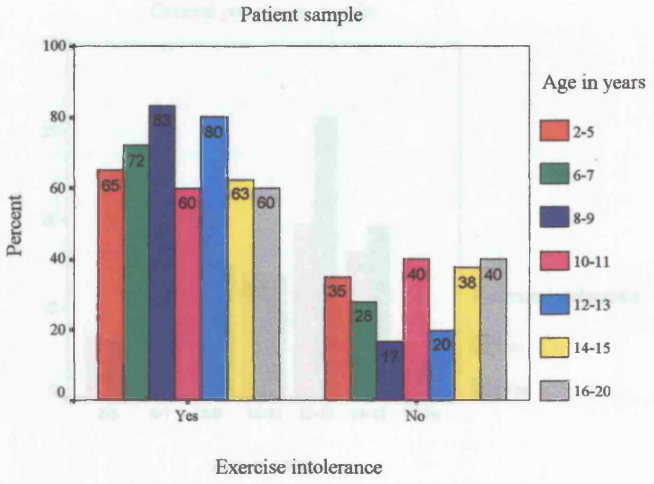


Table 4.1.36. shows the number of Gp subjects who reported exercise intolerance in the various age categories.

Table 4.1.36: Exercise intolerance
Effect of age
Gp group

Exercise intolerance / Age in years	Yes	No	Total
2-7	12	303	315
8-11	22	412	434
12-20	39	452	491
Total	73	1167	1240

Figure 4.1.38 shows the distribution of reports of exercise intolerance across the various age categories of the Gp group, highlighting the percentage of reports of exercise intolerance from each age category.

Figure 4.1.38: Exercise intolerance in various age categories

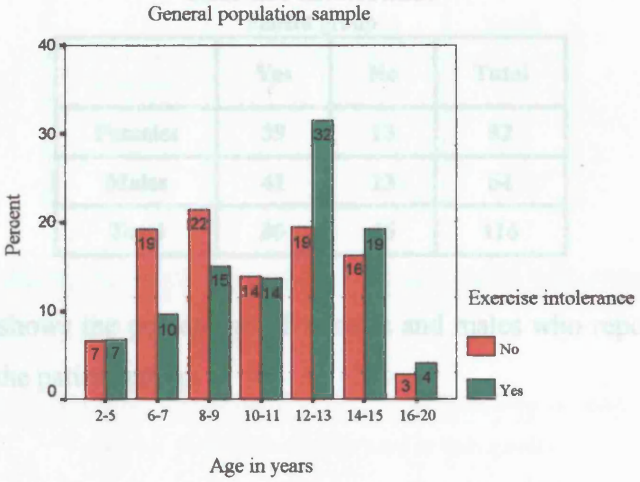
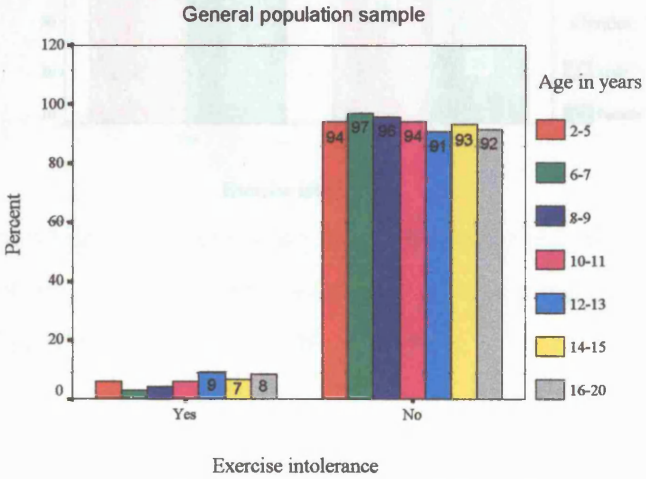


Figure 4.1.39 shows the distribution of Gp subjects who reported exercise intolerance in each age category, highlighting the percentage of reports of exercise intolerance within each age category.

Figure 4.1.39: Exercise intolerance in each age category



Chi squared test applied to both groups revealed that significantly more patients reported exercise intolerance than Gp subjects in all the age categories ($p = 0.000$).

4.1.5.4. Effect of gender

Table 4.1.37. shows the number of subjects of each gender within the patient group, who reported exercise intolerance.

Table 4.1.37: Effect of gender
Exercise intolerance
Patient group

	Yes	No	Total
Females	**39**	**13**	**52**
Males	**41**	**23**	**64**
Total	**80**	**36**	**116**

Figure 4.1.40 shows the percentage of females and males who reported exercise intolerance in the patient group.

Figure 4.1.40: Exercise intolerance in both genders

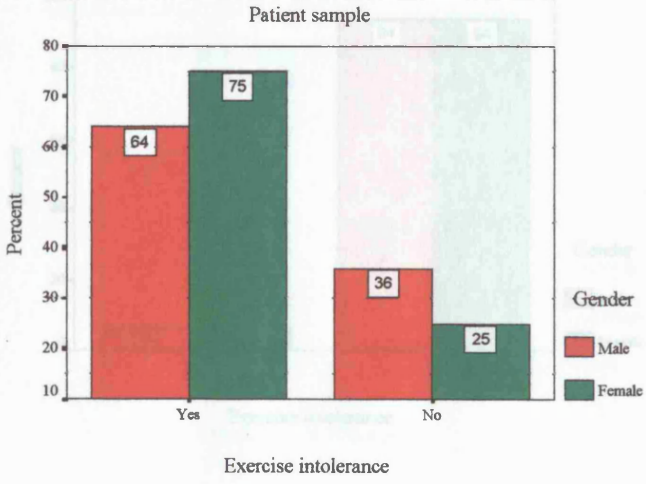


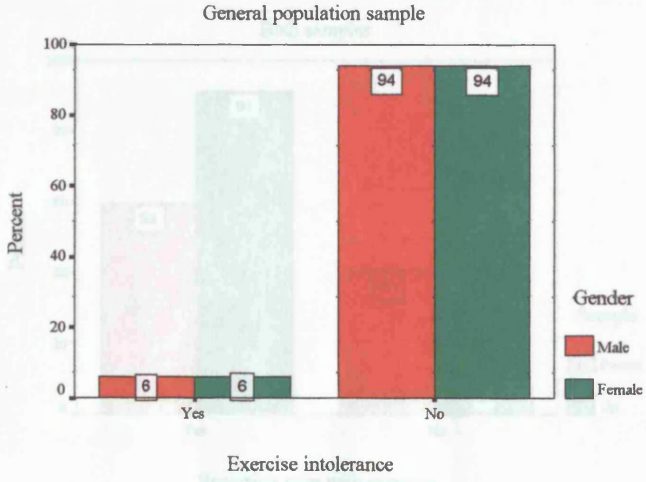
Table 4.1.38. shows the number of subjects of each gender within the Gp group, who reported exercise intolerance.

Table 4.1.38: Effect of gender
Exercise intolerance
Gp group

	Yes	No	Total
Females	**37**	**575**	**612**
Males	**36**	**570**	**606**
Total	**73**	**1145**	**1218**

Figure 4.1.41 shows the percentage of females and males who reported exercise intolerance in the Gp group.

Figure 4.1.41: Exercise intolerance in both genders



Chi squared test revealed no significant difference in the prevalence of exercise intolerance between the two genders within the patient group (χ^2 = 1.604, p = 0.205) or within the Gp group (χ^2 = 0.006, p = 0.938).

4.1.5.5. Reporting leg pain with exercise

Table 4.1.39. shows the number of subjects who reported leg pain with exercise in both groups, excluding cases of leg pain due to a known aetiology.

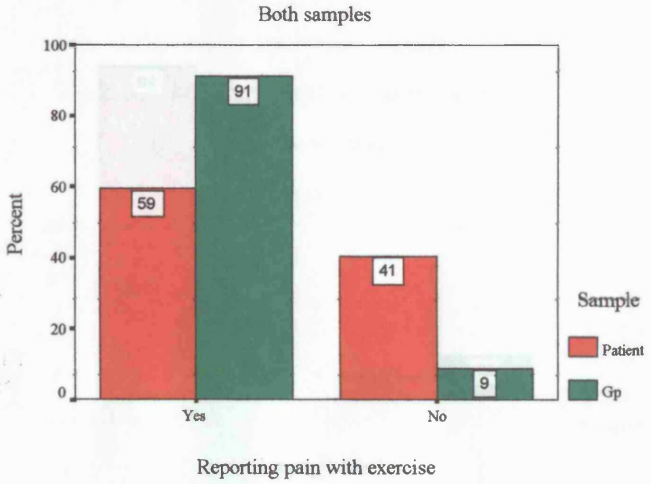
Table 4.1.39: Leg pain with exercise

Both groups

	Yes	No	Total
Patients	**47**	**32**	**79**
Gps	**52**	**5**	**57**
Total	**99**	**37**	**136**

Figure 4.1.42 shows the percentage of subjects in each sample who reported leg pain with exercise.

Figure 4.1.42: Reporting leg pain with exercise



Chi squared test applied to both groups showed that significantly more Gp subjects report leg pain with exercise than patients ($\chi^2 = 16.837$, $p = 0.000$).

4.1.5.6. Lagging behind during walking

Table 4.1.40. shows the number of subjects who lagged behind during walking in both groups, after excluding cases of leg pain due to a known aetiology.

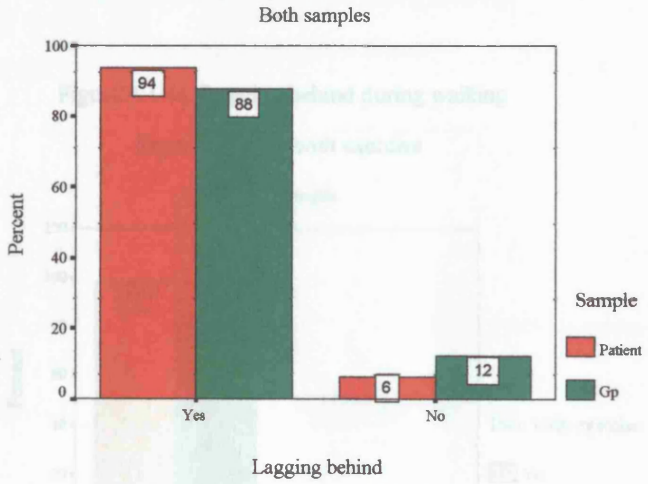
Table 4.1.40: Lagging behind with exercise

Both groups

	Yes	No	Total
Patients	**74**	**5**	**79**
Gp	**50**	**7**	**57**
Total	**124**	**12**	**136**

Figure 4.1.43 shows the percentage of subjects in each sample who lagged behind during walking.

Figure 4.1.43: Lagging behind during walking



Chi square test applied to both groups revealed no significant difference between the two groups in the prevalence of lagging behind during walking ($\chi^2 = 1.548$, p = 0.227).

4.1.5.7. Lagging behind during walking without reporting PUA

Table 4.1.41. shows the number of patients who lagged behind during walking without reporting PUA.

Table 4.1.41: Lagging behind with exercise

Reporting PUA with exercise

Patient groups

Lagging / Leg pain	Yes	No	Total
Yes	46	1	47
No	27	4	31
Total	73	5	78

Figure 4.1.44 shows that the majority of patients who did not complain of leg pain with exercise lagged behind during walking.

Figure 4.1.44: Lagging behind during walking

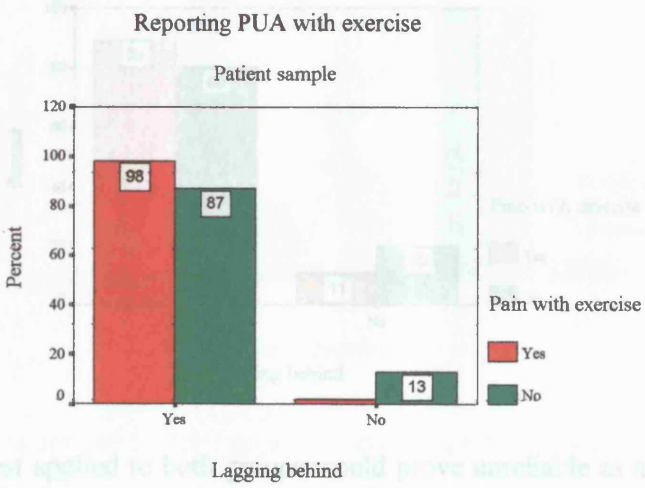


Table 4.1.42. shows the number of Gp subjects who lagged behind during walking without reporting PUA.

Table 4.1.42: Lagging behind with exercise

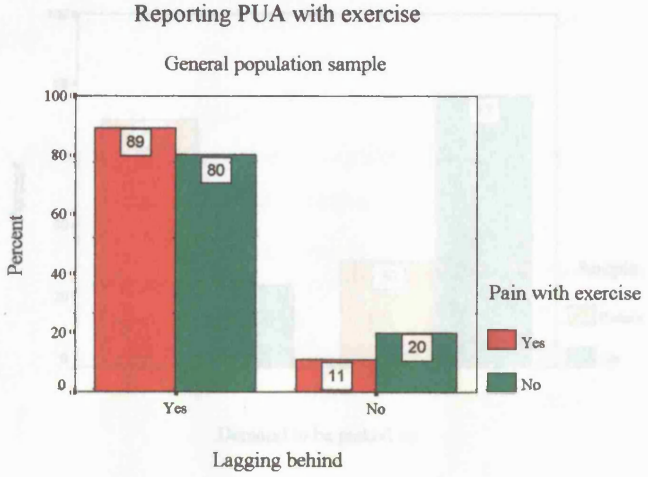
Reporting PUA with exercise

Gp groups

Lagging / Leg pain	Yes	No	Total
Yes	42	5	47
No	4	1	5
Total	46	6	52

Figure 4.1.45 shows that half the Gp subjects who did not complain of leg pain with exercise lagged behind during walking.

Figure 4.1.45: Lagging behind during walking



Chi squared test applied to both groups would prove unreliable as a result of the presence of low frequencies.

4.1.5.8. Demanding to be picked up

Table 4.1.43. shows the number of subjects who demanded to be picked up during walking in both groups.

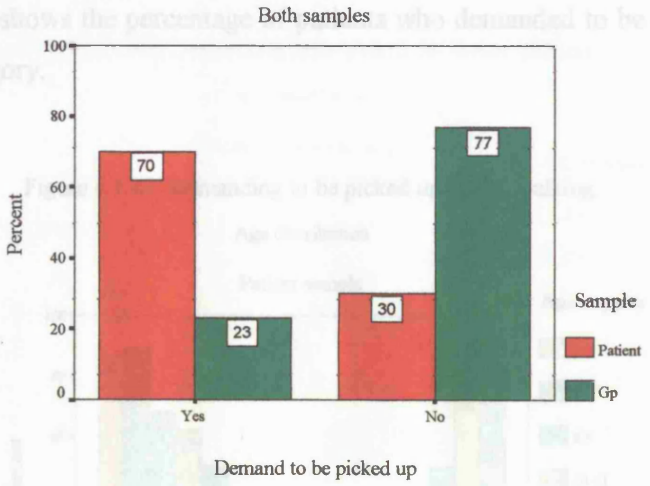
Table 4.1.43: Demanding to be picked up during walking

Both groups

	Yes	No	Total
Patients	**54**	**23**	**77**
Gp	**12**	**40**	**52**
Total	**66**	**63**	**129**

Figure 4.1.46 shows the percentage of subjects in each sample that demanded to be picked up during walking.

Figure 4.1.46: Demanding to be picked up



Chi squared test applied to both groups revealed that significantly more patients demanded to be picked up during walking than Gp subjects (χ^2 = 27.503, p = 0.000).

Age distribution

Table 4.1.44. shows the number of patients who demanded to be picked up during walking in the various age categories. Some age groups are combined to avoid the detrimental effect of low frequencies on the Chi squared test

Table 4.1.44: Demanding to be picked up during walking
Age distribution
Patient group

Age group	Yes	No	Total
2-7	28	4	32
8-11	20	10	30
12-20	5	10	15
Total	54	24	77

Figure 4.1.47 shows the percentage of patients who demanded to be picked up in each age category.

Figure 4.1.47: Demanding to be picked up during walking

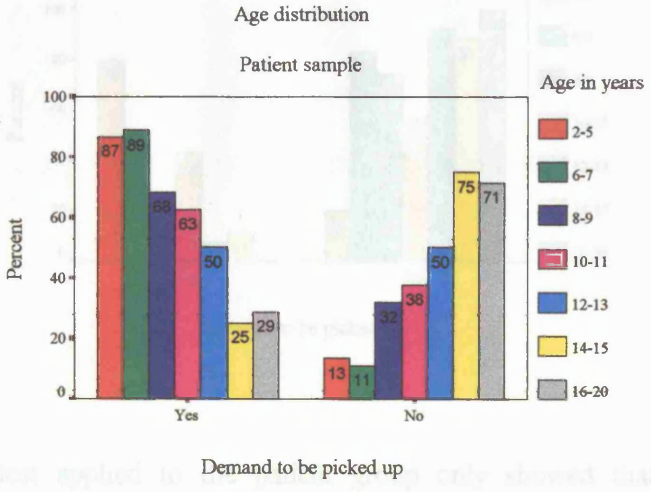


Table 4.1.45. shows the number of Gp subjects who demanded to be picked up in the various age categories. Some age groups are combined to avoid the detrimental effect of low frequencies on the Chi squared test

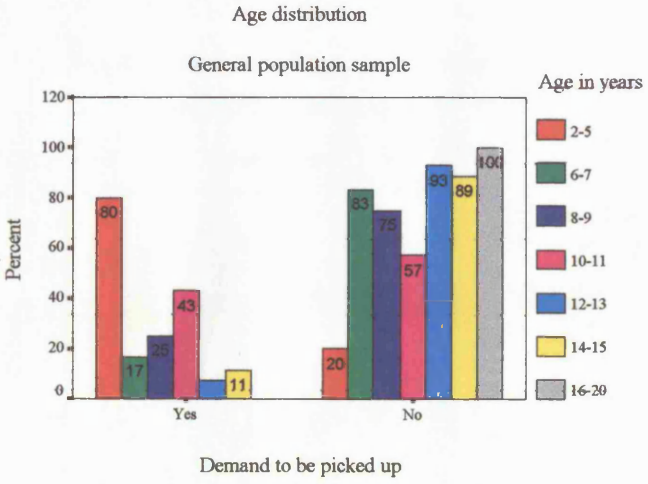
Table 4.1.45: Demanding to be picked up in the various age categories

Gp group

Age group	Yes	No	Total
2-7	5	6	11
8-11	5	10	15
12-20	2	24	26
Total	12	40	52

Figure 4.1.48 shows the percentage of Gp subjects who demanded to be picked up in each age category.

Figure 4.1.48: Demanding to be picked up during walking



Chi squared test applied to the patient group only showed that there is a significant difference in the prevalence of demanding to be picked up during walking in all age categories:

2-7 > 8-11 ($\chi^2 = 4.091$, $p = 0.043$)

2-7 > 12-20 ($\chi^2 = 14.851$, $p = 0.000$)

8-11 > 12-20 ($\chi^2 = 4.500$, $p = 0.034$)

Chi squared test applied to the Gp group only showed that there is a significant difference in the prevalence of demanding to be picked up during walking between the following age categories:

2-7 > 12-20 ($\chi^2 = 7.186$, $p = 0.007$)

8-11 > 12-20 ($\chi^2 = 4.417$, $p = 0.036$)

Chi squared test applied to both groups showed that significantly more patients than Gp subjects demand to be picked up during walking, in all age categories:

2-7 ($\chi^2 = 8.445$, $p = 0.004$)

8-11 ($\chi^2 = 4.500$, $p = 0.034$)

12-20 ($\chi^2 = 4.417$, $p = 0.036$)

4.1.5.9. Demanding to be picked up during walking without reporting leg pain

Table 4.1.46. shows the number of patients who demanded to be picked up during walking but did not report of leg pain during exercise, after excluding cases of pain due to a known aetiology.

Table 4.1.46: Demanding to be picked up

Reporting PUA with exercise

Patient groups

Picked up / PUA	Yes	No	Total
Yes	31	17	48
No	24	11	35
Total	55	28	83

Figure 4.1.49 shows that 69% of the patients who did not report PUA during exercise demanded to be picked up during walking.

Figure 4.1.49: Demanding to be picked up

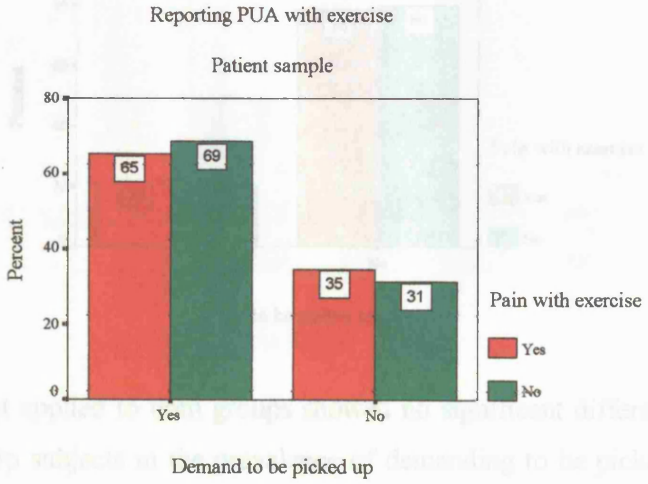


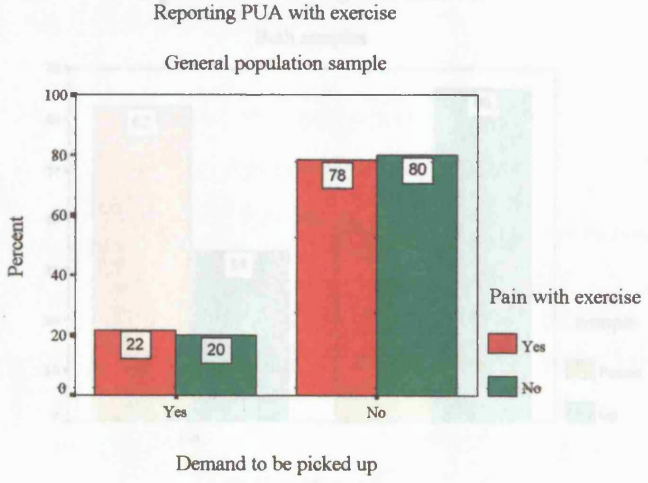
Table 4.1.47. shows the number of Gp subjects who demanded to be picked up during walking but did not report PUA during exercise.

Table 4.1.47: Demanding to be picked up
Reporting PUA with exercise
Gp groups

Picked up PUA	Yes	No	Total
Yes	8	29	37
No	1	4	5
Total	9	33	42

Figure 4.1.50 shows that 20% the Gp subjects who did not report PUA with exercise demanded to be picked up during walking.

Figure 4.1.50: Demanding to be picked up



Chi square test applied to both groups showed no significant difference between patients and Gp subjects in the prevalence of demanding to be picked up during walking without reporting PUA ($\chi^2 = 3.437$, $p = 0.064$).

4.1.5.10. Crying during exercise

Table 4.1.48. shows the number of patients and Gp subjects who cried during exercise.

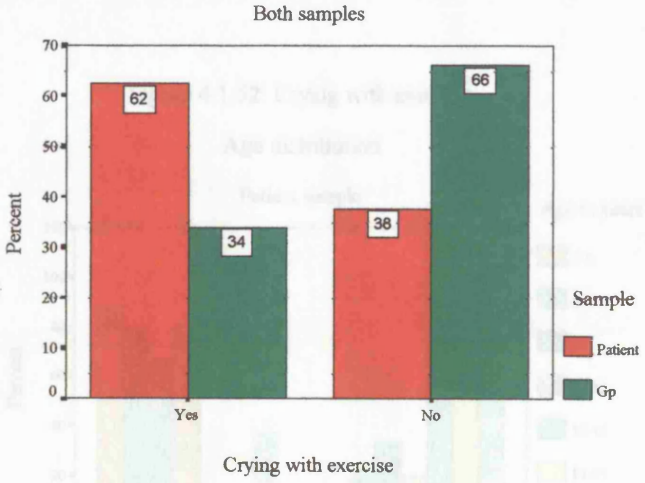
Table 4.1.48: Crying during exercise

Both groups

	Yes	No	Total
Patients	**53**	**32**	**85**
Gp	**19**	**37**	**56**
Total	**72**	**69**	**141**

Figure 4.1.51 shows the percentage of patients and Gp subjects who cried during exercise.

Figure 4.1.51: Crying with exercise



Chi squared test applied to both groups revealed that significantly more patients cried during exercise than Gp subjects. ($\chi^2 = 10.915$, $p = 0.001$).

Age distribution

Table 4.1.49. shows the number of patients who cried during exercise in the various age categories. Some age groups are combined to avoid the detrimental effect of low frequencies on the Chi squared test

Table 4.1.49: Crying during exercise
Age distribution

Patient group

Age group	Yes	No	Total
2-7	25	5	30
8-11	22	9	31
12-20	3	13	16
Total	50	27	77

Figure 4.1.52 shows the percentage of patients who cried during exercise in each age category.

Figure 4.1.52: Crying with exercise

Age distribution

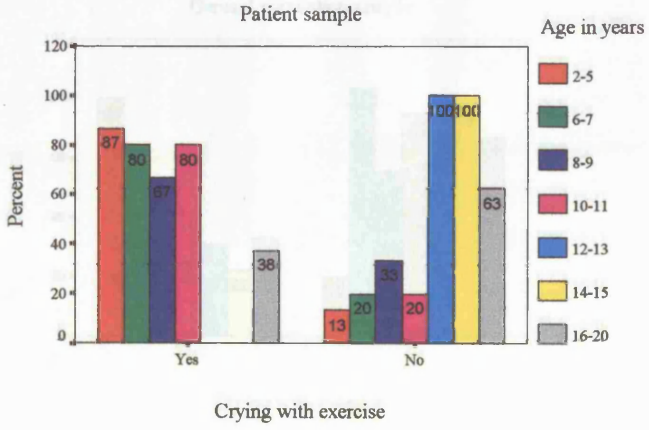


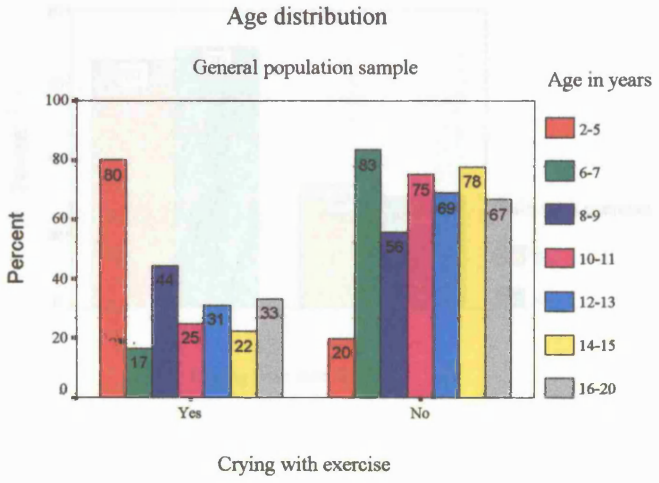
Table 4.1.50. shows the number of Gp subjects who cried during exercise in the various age categories. Some age groups are combined to avoid the detrimental effect of low frequencies on the Chi squared test

Table 4.1.50: Crying during exercise
Age distribution
Gp group

Age group	Yes	No	Total
2-7	5	6	11
8-11	6	11	17
12-20	8	20	28
Total	19	37	56

Figure 4.1.53 shows the percentage of Gp subjects who cried during exercise in each age category.

Figure 4.1.53: Crying with exercise



Chi squared test applied to both groups showed that significantly more patients cry during exercise than Gp subjects in the 2-5 years age category ($\chi^2 = 5.883$, $p = 0.015$) and the 8-11 years age category ($\chi^2 = 5.749$, $p = 0.017$).

4.1.5.11. Crying without reporting leg pain during exercise

Table 4.1.51. shows the number of patients who cried without reporting leg pain during exercise, after excluding cases of pain due to known aetiology.

Table 4.1.51: Crying during exercise
Reporting leg pain during exercise

Patient group

Crying / Leg pain	Yes	No	Total
Yes	30	14	44
No	19	12	31
Total	49	26	75

Figure 4.1.54 shows the percentage of patients who cried without complaining of leg pain during exercise.

Figure 4.1.54: Crying with exercise

Reporting leg pain with exercise

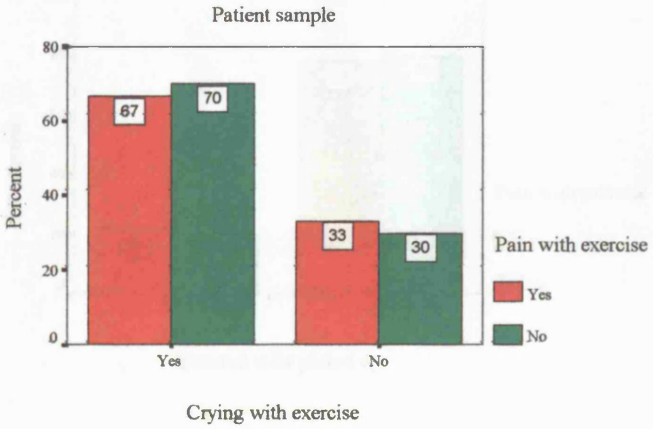


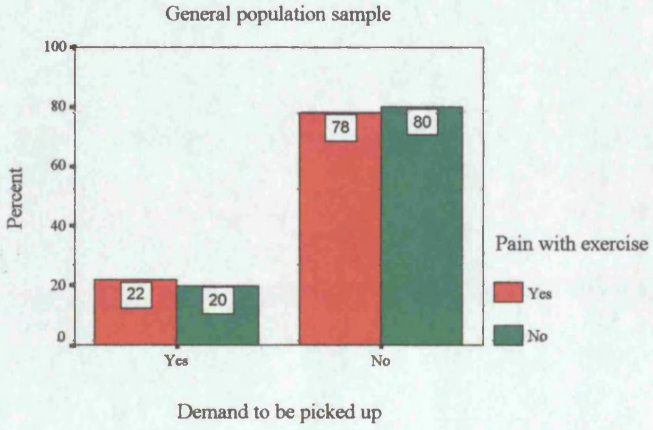
Table 4.1.52. shows the number of Gp subjects who cried without complaining of leg pain during exercise, after excluding cases of pain due to known aetiology.

Table 4.1.52: Crying during exercise
Complaining of leg pain during exercise
Gp group

Crying / Leg pain	Yes	No	Total
Yes	15	29	44
No	1	4	5
Total	16	33	49

Figure 4.1.55 shows the percentage of Gp subjects who cried without reporting leg pain during exercise.

Figure 4.1.55: Crying with exercise
Reporting leg pain with exercise



Chi squared test applied to both groups no significant difference between patients and Gp subjects in the prevalence of crying without reporting leg pain during exercise ($\chi^2 = 2.159$, $p = 0.142$).

4.1.5.12 Summary

- Significantly more patients with 22q11 deletion report exercise intolerance than children and adolescents of the general population (Gp).
- The peak age for exercise intolerance in patients with 22q11 deletion is 8-9 years old.
- The peak age for exercise intolerance in the Gp is 12-13 years old.
- There is equal gender prevalence for exercise intolerance in both populations.
- Significantly more Gp subjects report leg pain with exercise than patients.
- Significantly more patients demand to be picked up during walking than Gp subjects.
- Data analysis does not support the notion that patients may not report an existing pain that may cause exercise intolerance.

4.2. Results of the clinical study

4.2.1. The Sample

A sample of patients with 22q11 deletion, confirmed by Fluorescent In situ Hybridisation (FISH) test, was subjected to a standard battery of clinical tests. Patients included in this sample were identified from the sources listed in section 3.4.1.1. and were opportunistically selected regardless of gender or age. In all, 108 patients were examined and treated. Twenty four cases were excluded in accordance with the exclusion criteria explained in section 3.4.2.2.1.

Data analysis therefore, includes 84 patients, 41 females and 43 males between the ages of 2 and 23 years (Mean 8.12, S.D. 4.39).

4.2.2. History analysis

4.2.2.1. Leg pain

4.2.2.1.1. Reporting leg pain

Frequency analysis showed that 61 out of 84 patients (72.6%) reported leg pain due to an unknown aetiology. Subsequent results in this section (4.2.2.1.) will only include the 61 cases that reported leg pain.

4.2.2.1.2. Side of leg pain

Table 4.2.1. shows the distribution of patients across the various "Side of leg pain" categories. The category labelled "Alternate" refers to pain experienced in one limb at one occasion and affecting the contralateral limb in the subsequent episode.

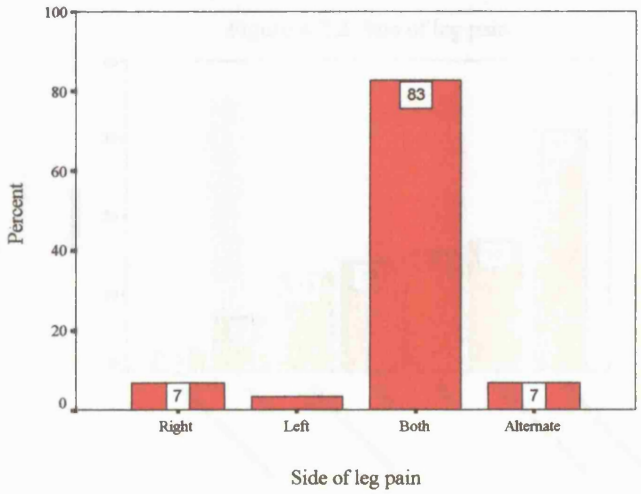
Table 4.2.1: Side of leg pain

Both samples

Side of pain	Patients
Right	**4**
Left	**2**
Bilateral	**48**
Alternate	**4**
Total	**58**

Figure 4.2.1 shows that in the majority of patients, leg pain was reported bilaterally.

Figure 4.2.1: Side of leg pain



4.2.2.1.3. Site of leg pain

Table 4.2.2. shows the distribution of patients across the various "Site of leg pain" categories.

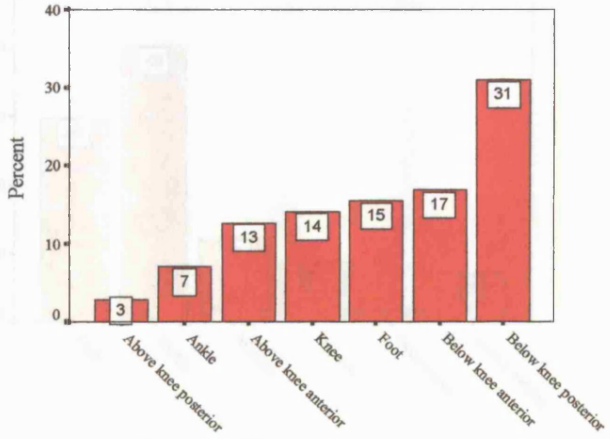
Table 4.2.2: Site of leg pain

Site of pain	Patients
Above knee posteriorly	2
Ankle	5
Above knee anteriorly	9
Knee	10
Foot	11
Below knee anteriorly	12
Below knee posteriorly	22
Total	71*

* Some patients reported leg pain in more than one site

Figure 4.2.2. shows the percentage of patients who reported the various sites of leg pain.

Figure 4.2.2: Site of leg pain



4.2.2.1.4. Frequency of leg pain episodes

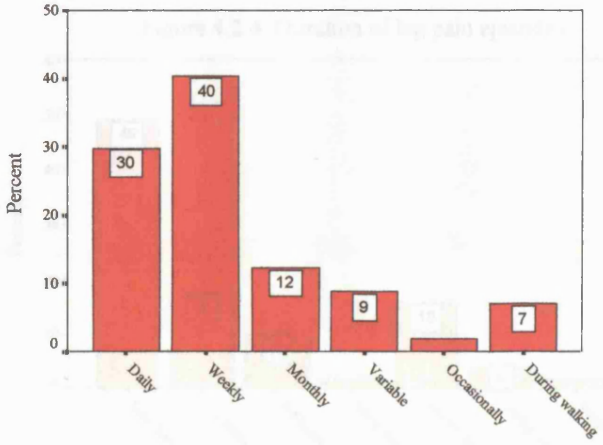
Table 4.2.3. shows the distribution of patients across the various "Frequency of leg pain episodes" categories.

Table 4.2.3: Frequency of leg pain episodes

Frequency	Patients
Daily	17
Weekly	23
Monthly	7
Variable	5
Occasionally	1
During walking	4
Total	57

Figure 4.2.3. shows the percentage of patients who reported the various "Frequency of leg pain episodes" category.

Figure 4.2.3: Frequency of leg pain episodes



4.2.2.1.5. Duration of leg pain episodes

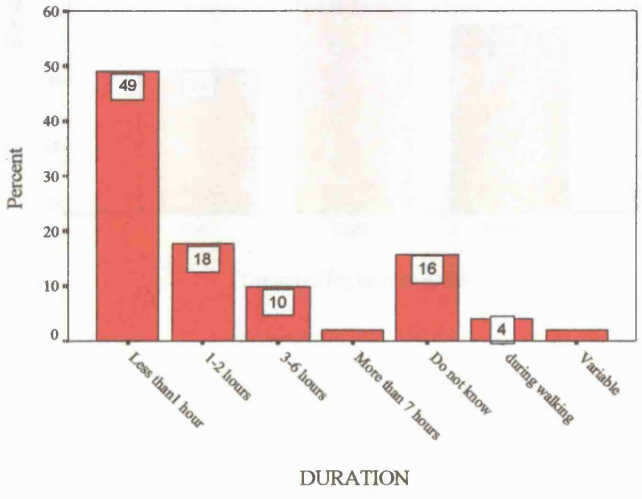
Table 4.2.4. shows the distribution of patients across the various "Duration of leg pain episodes" categories.

Table 4.2.4: Duration of leg pain episodes

Duration	Patients
Less than an hour	25
1-2 hours	9
3-6 hours	5
More than 7 hours	1
Do not know	8
During walking	2
Variable	1
Total	51

Figure 4.2.4. shows the percentage of patients who reported the various "Duration of leg pain episodes" categories.

Figure 4.2.4: Duration of leg pain episodes



4.2.2.1.6. Timing of leg pain episodes

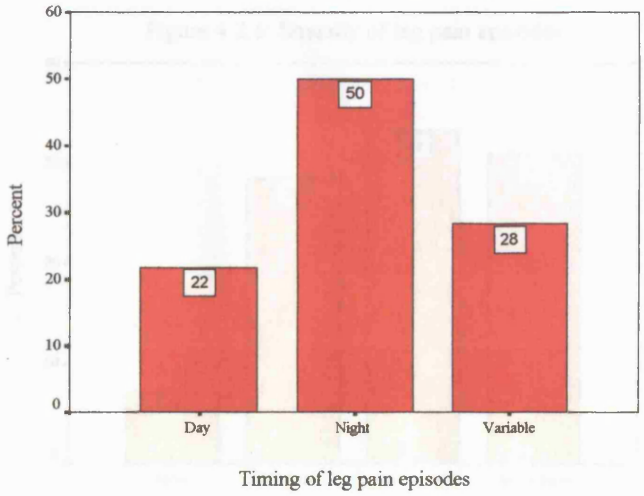
Table 4.2.5. shows the distribution of patients across the various "Timing of leg pain episodes" categories.

Table 4.2.5: Timing of leg pain episodes

Timing	Patients
Day	10
Night	23
Variable	13
Total	46

Figure 4.2.5. shows the percentage of patients who reported the various "Timing of leg pain episodes" categories.

Figure 4.2.5: Timing of leg pain episodes



4.2.2.1.7. Severity of leg pain episodes

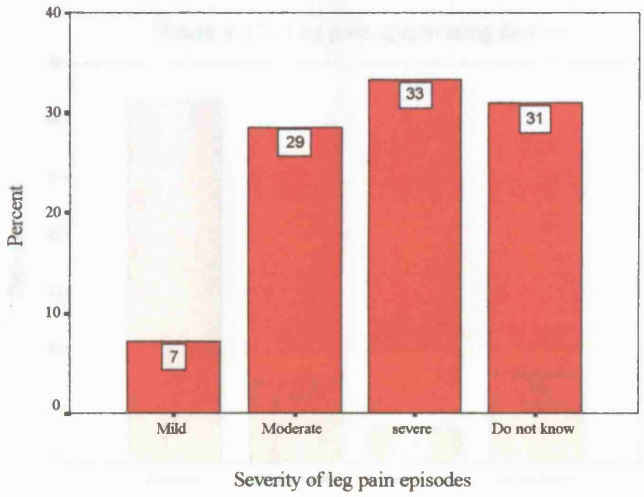
Table 4.2.6. shows the distribution of patients across the various "Severity of leg pain episodes" categories.

Table 4.2.6: Severity of leg pain episodes

Severity	Patients
Mild	3
Moderate	12
Severe	14
Do not know	13
Total	42

Figure 4.2.6. shows the percentage of patients who reported the various "Severity of leg pain episodes" categories.

Figure 4.2.6: Severity of leg pain episodes



4.2.2.1.8. Leg pain aggravating factors

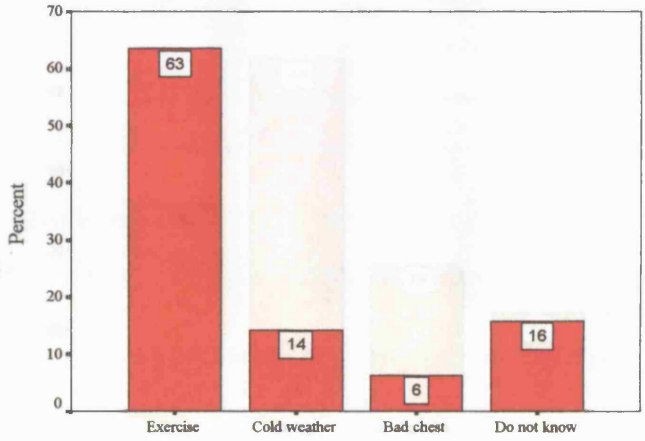
Table 4.2.7. shows the distribution of patients across the various "Leg pain aggravating factors" categories. One patient may have more than one aggravating factor.

Table 4.2.7: Aggravating factors

Aggravating factor	Patients
Exercise	40
Cold weather	9
Bad chest	4
Do not know	10
Total	63

Figure 4.2.7. shows the percentage of patients who reported the various "Leg pain aggravating factors" category.

Figure 4.2.7: Leg pain aggravating factors



4.2.2.1.9. Leg pain relieving factors

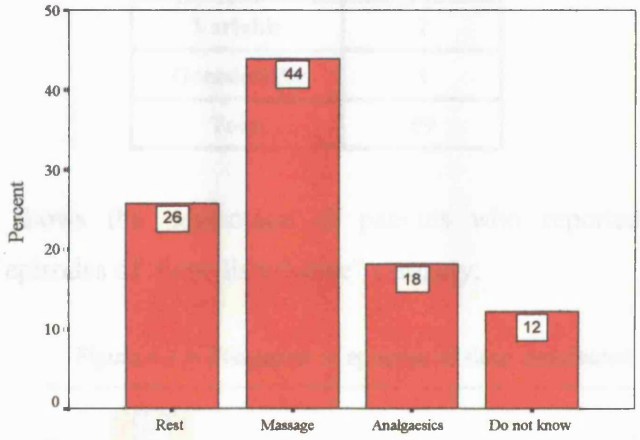
Table 4.2.8. shows the distribution of patients across the various "Leg pain relieving factors" categories. One patient may have more than one relievung factor.

Table 4.2.8: Relieving factors

Relieving factor	Patients
Rest	17
Massage	29
Analgaesics	12
Do not know	8
Total	66

Figure 4.2.8. shows the percentage of patients who reported the various "Leg pain relieving factors" category.

Figure 4.2.8: Leg pain relieving factors



4.2.2.2. Sleep disturbance

4.2.2.2.1. Reports of sleep disturbance

Frequency analysis showed that 60 out of 82 patients (73.1%) reported sleep disturbance. Subsequent results in this section (4.2.2.2.) will only include the 60 cases that reported sleep disturbance.

4.2.2.2.2. Frequency of sleep disturbance episodes

Table 4.2.9. shows the distribution of patients across the various "Frequency of sleep disturbance episodes" categories.

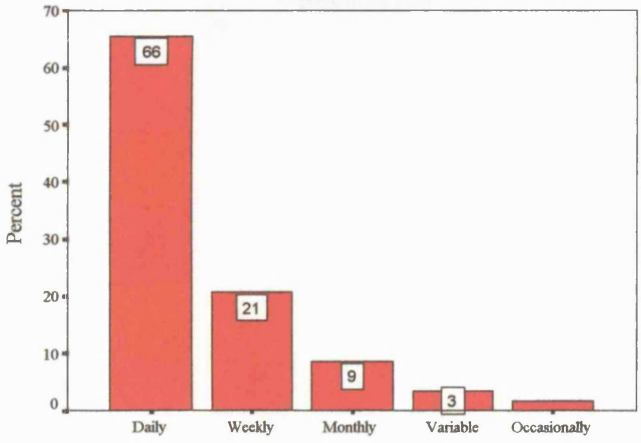
Table 4.2.9: Sleep disturbance

Frequency of episode

Frequency	Patients
Daily	39
Weekly	12
Monthly	5
Variable	2
Occasionally	1
Total	59

Figure 4.2.9. shows the percentage of patients who reported the various "Frequency of episodes of sleep disturbance" category.

Figure 4.2.9: Frequency of episodes of sleep disturbance



Frequency of episodes of sleep disturbance

4.2.2.2.3. Sleep disturbance with reporting leg pain

Table 4.2.10. shows the number of patients who reported leg pain during episodes of sleep disturbance.

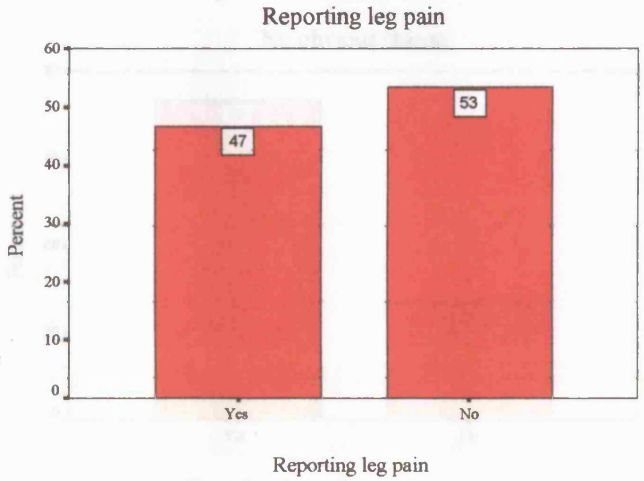
Table 4.2.10: Sleep disturbance

Reporting of leg pain

Leg pain	Patients
Yes	28
No	32
Total	60

Figure 2.4.10. shows the percentage of patients who reported leg pain during episodes of sleep disturbance

Figure 4.2.10: Sleep disturbance



4.2.2.2.4. Sleep disturbance for no obvious reasons

Table 4.2.11. shows the number of patients whose sleep was disturbed for no obvious reason.

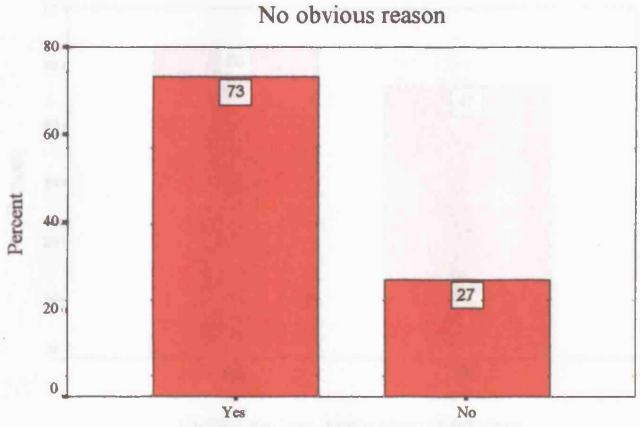
Table 4.2.11: Sleep disturbance

No obvious reason

Sleep disturbance no reason	Patients
Yes	41
No	15
Total	56

Figure 4.2.11. shows the percentage of patients who reported sleep disturbance for no obvious reason.

Figure 4.2.11: Sleep disturbance



4.2.2.2.5. Sleep disturbance with kicking the legs

Table 4.2.12. shows the number of patients who kicked their legs during episodes of sleep disturbance.

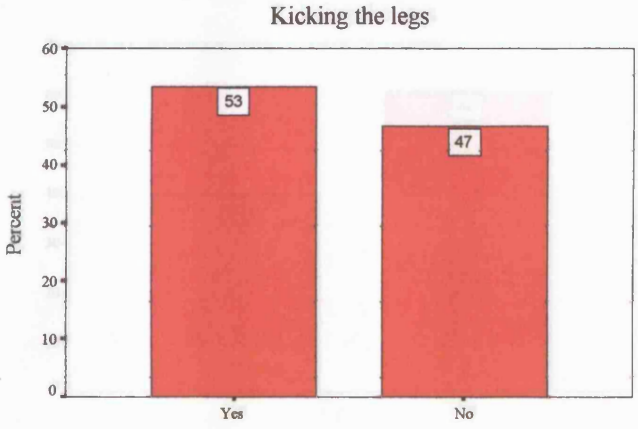
Table 4.2.12: Sleep disturbance

Kicking the legs

Leg kicking	Patients
Yes	31
No	27
Total	58

Figure 4.2.12. shows the percentage of patients who kicked their legs during episodes of sleep disturbance.

Figure 4.2.12: Sleep disturbance



4.2.2.2.6. Sleep disturbance with rubbing the legs

Table 4.2.13. shows the number of children rubbed their legs during episodes of sleep disturbance.

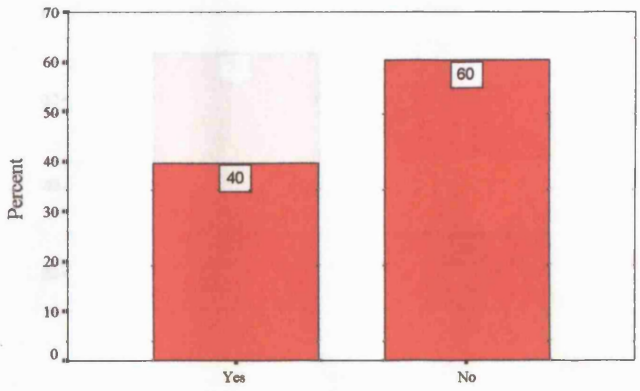
Table 4.2.13: Sleep disturbance with
Rubbing the legs

Leg kicking	Patients
Yes	23
No	35
Total	58

Figure 4.2.13. shows the percentage of patients who rubbed their legs during episodes of sleep disturbance.

Figure 4.2.13: Sleep disturbance

Rubbing the legs



Rubbing the legs during sleep disturbance

4.2.2.2.7. Sleep disturbance with crying

Table 4.2.14. shows the number of patients who cried during episodes of sleep disturbance.

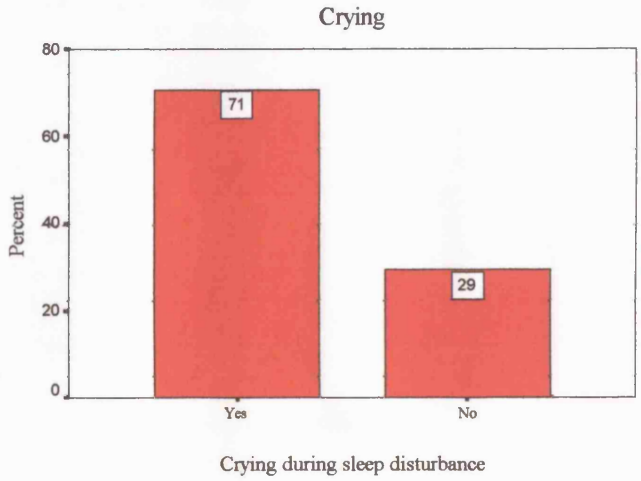
Table 4.2.14: Sleep disturbance

Crying

Leg kicking	Patients
Yes	41
No	17
Total	58

Figure 4.2.14. shows the percentage of patients who cried during episodes of sleep disturbance.

Figure 4.2.14: Sleep disturbance



4.2.2.3. Exercise intolerance

Exercise intolerance refers to the inability of the patient to exercise as much as others of similar age. Frequency analysis showed that 57 out of 81 patients (70.4%) reported exercise intolerance. Subsequent results in this section (4.2.2.3.) will only include the 57 cases that reported exercise intolerance.

4.2.2.3.1. Reporting leg pain during exercise

Table 4.2.15. shows the number of patients who reported leg pain during exercise.

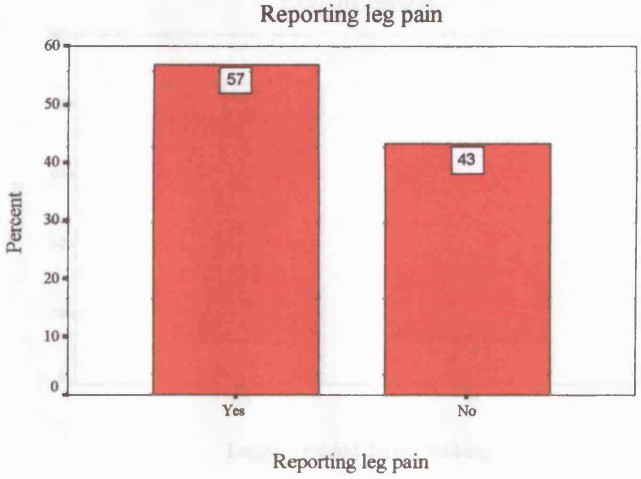
Table 4.2.15: Exercise intolerance

Reporting leg pain

Leg pain	Patients
Yes	25
No	19
Total	44

Figure 4.2.15. shows the percentage of patients who reported leg pain during exercise.

Figure 4.2.15: Exercise intolerance



4.2.2.3.2. Lagging behind during walking

Table 4.2.16. shows the number of patients who lagged behind during walking.

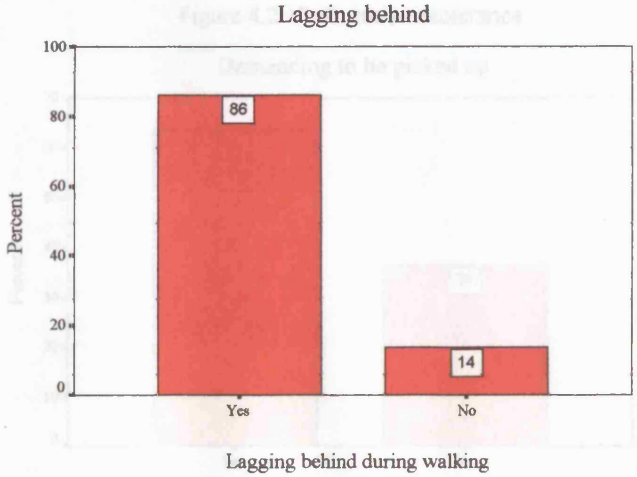
Table 4.2.16: Exercise intolerance

Lagging behind

Lagging behind	Patients
Yes	38
No	6
Total	44

Figure 4.2.16. shows the percentage of patients who lagged behind during walking.

Figure 4.2.16: Exercise intolerance



4.2.2.3.3. Demanding to be picked up during walking

Table 4.2.17. shows the number of patients who demanded to be picked up during walking.

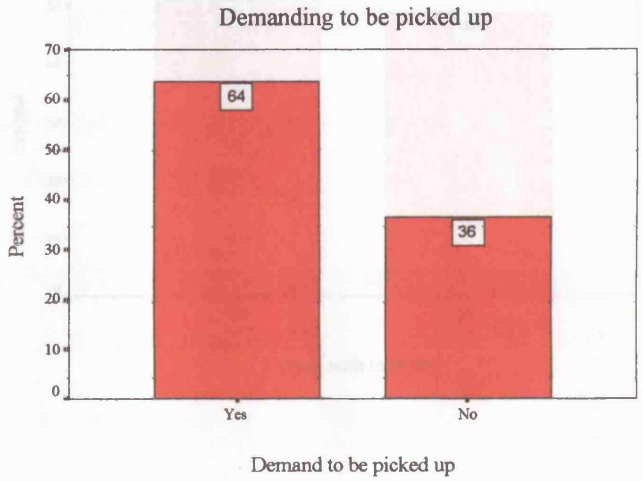
Table 4.2.17: Exercise intolerance

Demanding to be picked up

Demand to be picked up	Patients
Yes	28
No	16
Total	44

Figure 4.2.17. shows the percentage of patients who demanded to be picked up during walking.

Figure 4.2.17: Exercise intolerance



4.2.2.3.4. Crying during exercise

Table 4.2.18. shows the number of patients who cried during exercise.

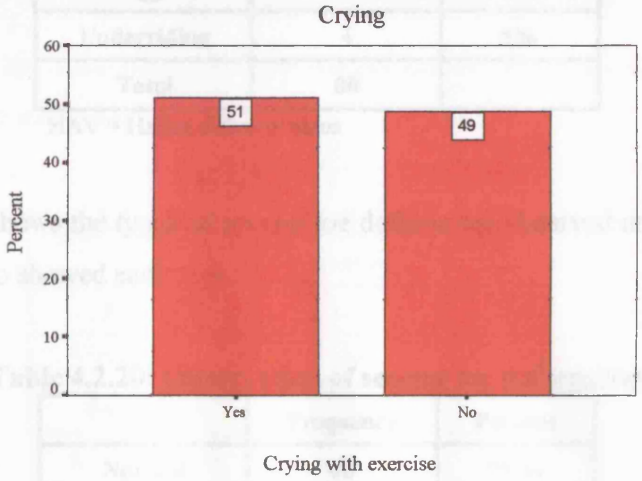
Table 4.2.18: Exercise intolerance

Crying

Crying	Patients	Percent
Yes	22	51%
No	21	49%
Total	43	

Figure 4.2.18. shows the percentage of patients who cried during walking.

Figure 4.2.18: Exercise intolerance



4.2.3. Biomechanical examination

4.2.3.1. Toe deformities

All listed observations apply bilaterally.

Table 4.2.19 shows the types of halux deformities observed and the number of patients who showed each type.

Table 4.2.19: Observation of hallux deformities

	Frequency	Percent
No deformity	**66**	**83%**
HAV	**6**	**8%**
Trigger	**4**	**5%**
Underriding	**4**	**5%**
Total	**80**	

HAV = Hallux abductovalgus

Table 4.2.20 shows the types of second toe deformities observed and the number of patients who showed each type.

Table 4.2.20: Observation of second toe deformities

	Frequency	Percent
Normal	**62**	**79.%**
Dorsiflexed	**10**	**13%**
Hammer	**2**	**3%**
Syndactyly	**1**	**1%**
Clawed	**3**	**4%**
Total	**78**	

Table 4.2.21 shows the types of third toe deformities observed and the number of patients who showed each type.

Table 4.2.21: Observation of third toe deformities

	Frequency	Percent
Normal	**57**	**72%**
Hammer	**1**	**1%**
Dorsiflexed	**1**	**1%**
Adductovarus	**10**	**13%**
Underriding	**2**	**3%**
Syndactyly	**1**	**1%**
Clawed	**7**	**9%**
Total	**79**	

Table 4.2.22 shows the types of fourth toe deformities observed and the number of patients who showed each type.

Table 4.2.22: Observation of fourth toe deformities

	Frequency	Percent
Normal	**41**	**52%**
Hammer	**1**	**1%**
Dorsiflexed	**1**	**1%**
Adductovarus	**29**	**37%**
Underriding	**1**	**1%**
Syndactyly	**1**	**1%**
Clawed	**5**	**6%**
Total	**79**	

Table 4.2.23 shows the types of fifth toe deformities observed and the number of patients who showed each type.

Table 4.2.23: Observation of fifth toe deformities

	Frequency	Percent
Normal	26	33%
Hammer	1	1%
Adductovarus	48	60%
Syndactyly	1	1%
Clawed	4	5%
Total	80	

4.2.3.2. Examination of the first ray

Table 4.2.24 shows the types of first ray deformities observed and the number of patients who showed each type.

Table 4.2.24: Observation of first ray deformities

	Frequency	Percent
Neutral	65	81%
Plantarflexed	14	18%
Dorsiflexed	1	1%
Total	80	

4.2.3.3. Examination of forefoot to rear foot alignment

Table 4.2.25 shows the number of patients with and without forefoot invertus.

Table4.2.25: Observation of the forefoot to rear foot alignment

	Frequency	Percent
Normal	74	96%
F/F invertus	3	4%
Total	77	

4.2.3.4. Observation of subtalar joint varus

Table 4.2.26 shows the number of patients with and without subtalar joint varus.

Table 4.2.26: Observation of subtalar joint varus

	Frequency	Percent
Yes	16	22%
No	58	78%
Total	74	

4.2.3.1.5. Observation of rear foot varus

Table 4.2.27 shows the number of patients with and without rear foot varus.

Table 4.2.27: Observation rear foot varus

	Frequency	Percent
Yes	19	28%
No	50	73%
Total	69	

4.2.3.5. Observation of subtalar joint pronation

Table 4.2.28 shows the number of patients with and without excessive subtalar joint pronation.

Table 4.2.28: Observation of subtalar joint pronation

Pronation	Frequency	Percent
Yes	65	84%
No	12	16%
Total	77	

4.2.3.6. Examination of ankle joint range of motion

Table 4.2.29 shows the types of ankle joint abnormalities of range of motion and the number of patients who showed each type.

Table 4.2.29: Examination of the ankle joint range of motion

	Frequency	Percent
Normal	21	26%
Soft tissue*	60	73%
Bonny*	1	1%
Total	82	100%

* = Ankle equines

4.2.3.7. Tibial alignment

Table 4.2.30 shows the various types of tibial alignments and the number of patients who showed each type.

Table 4.2.30: Observation of tibial position

	Frequency	Percent
Neutral	44	57%
Varum	21	27%
Valgum	12	16%
Total	77	

4.2.3.8. Limb length discrepancy

Table 4.2.31 shows the number of patients who were observed to have limb length discrepancy.

Table 4.2.31: Observation limb length discrepancy

	Frequency	Percent
None	36	69%
Right shorter	13	25%
Left shorter	3	6%
Total	52	

4.2.3.9. Intoeing during gait

Table 4.2.32 shows the number of patients who showed intoeing during gait

Table 4.2.32: Observation of intoeing during gait

	Frequency	Percent
No	48	83%
Yes	10	17%
Total	58	

4.2.3.10. Observation of the Tibialis Posterior tendon

Table 4.2.33 shows the number of patients with an anteriorly displaced Tibialis Posterior tendon, coursing medial to, rather than posterior to the medial mallaeolus.

Table 4.2.33: Observation of Tibialis posterior tendon

	Frequency	Percent
Anteriorly displaced	43	57%
Normal	15	20%
Not seen	17	23%
Total	75	100%

4.2.4 Symptoms and signs

4.2.4.1 Adductovarus 4th toes

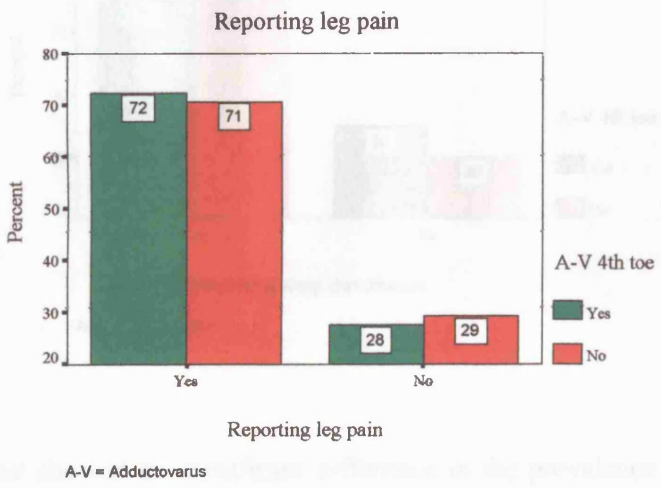
Table 4.2.34 shows the number of patients with adductovarus 4th toes who reported leg pain.

Table 4.2.34: Adductovarus 4th toe
Reporting leg pain

Reporting leg pain	Adductovarus 4th toes	
	Yes	No
Yes	21	29
No	8	12
Total	29	41

Figure 4.2.19 shows the relationship between adductovarus 4th toes and reporting leg pain.

Figure 4.2.19: Adductovarus 4th toes



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without adductovarus 4th toes ($\chi^2 = 0.024$, p = 0.878).

Table 4.2.35 shows the number of patients with adductovarus 4th toes who reported sleep disturbance.

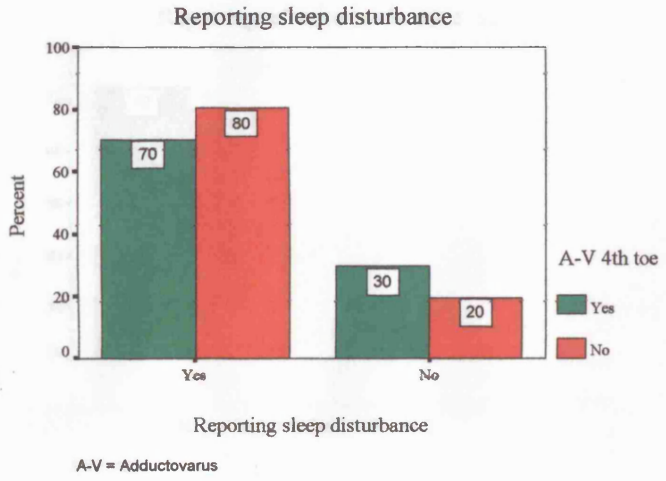
Table 4.2.35: Adductovarus 4th toe

Reporting sleep disturbance

Reporting sleep disturbance	Adductovarus 4th toes	
	Yes	No
Yes	19	33
No	10	8
Total	29	41

Figure 4.2.20 shows the relationship between adductovarus 4th toes and reporting sleep disturbance.

Figure 4.2.20: Adductovarus 4th toes



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without adductovarus 4th toes (χ^2 = 1.993, p = 0.158).

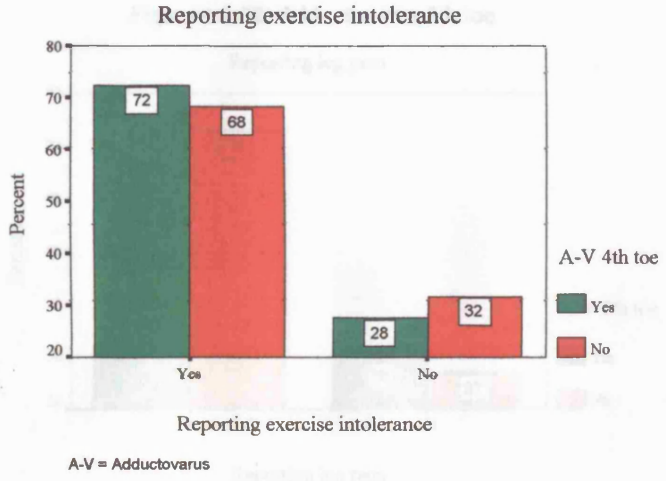
Table 4.2.36 shows the number of patients with adductovarus 4th toes who reported exercise intolerance.

Table 4.2.36: Adductovarus 4th toe
Reporting exercise intolerance

Reporting exercise intolerance	Adductovarus 4th toes	
	Yes	No
Yes	8	13
No	21	28
Total	29	41

Figure 4.2.21 shows the relationship between adductovarus 4th toes and reporting sleep disturbance.

Figure 4.2.21: Adductovarus 4th toes



Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without adductovarus 4th toes (χ^2 = 0.137, p = 0.711).

4.2.4.2 Adductovarus 5th toes

Table 4.2.37 shows the number of patients with adductovarus 5th toes who reported leg pain.

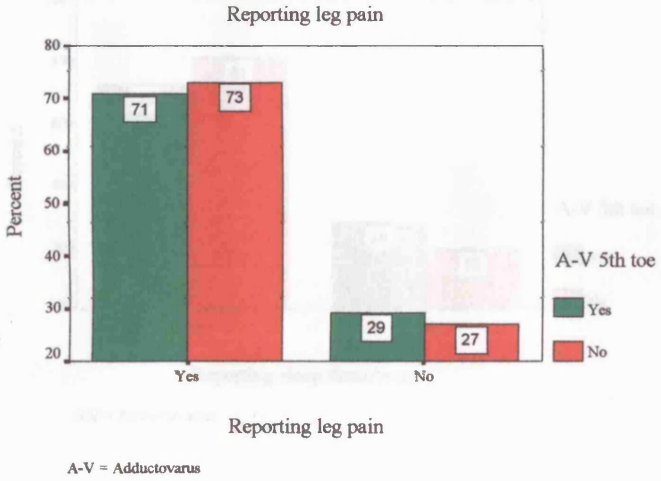
Table 4.2.37: Adductovarus 5th toe

Reporting leg pain

Reporting leg pain	Adductovarus 5th toes	
	Yes	No
Yes	34	19
No	14	7
Total	48	26

Figure 4.2.22 shows the relationship between adductovarus 5th toes and reporting leg pain.

Figure 4.2.22: Adductovarus 5th toe



A-V = Adductovarus

Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without adductovarus 5th toes ($\chi^2 = 0.042$, $p = 0.838$).

Table 4.2.38 shows the number of patients with adductovarus 5th toes who reported sleep disturbance.

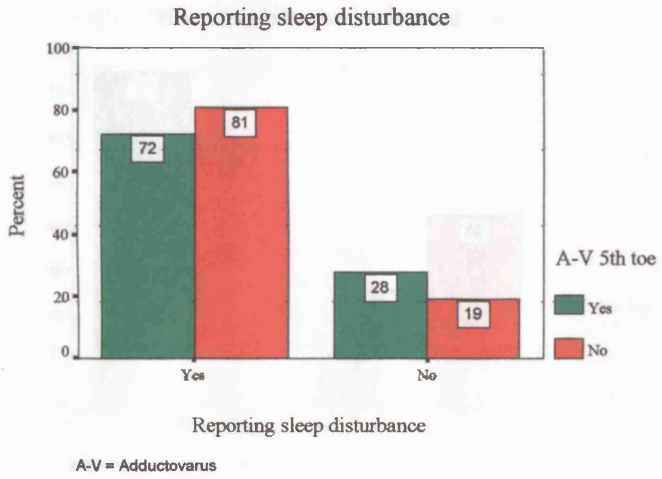
Table 4.2.38: Adductovarus 5th toe

Reporting sleep disturbance

Reporting sleep disturbance	Adductovarus 5th toes	
	Yes	No
Yes	34	21
No	13	5
Total	47	26

Figure 4.2.23 shows the relationship between adductovarus 4th toes and reporting sleep disturbance.

Figure 4.2.23: Adductovarus 5th toes



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without adductovarus 5th toes (χ^2 = 0.640, p = 0.424).

Table 4.2.39 shows the number of patients with adductovarus 5th toes who reported exercise intolerance.

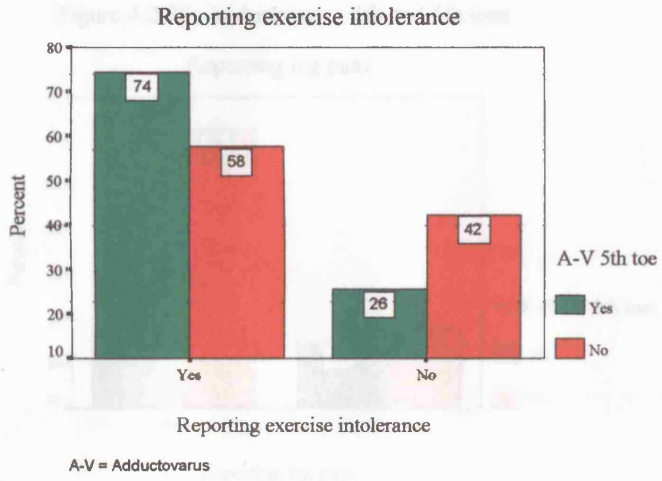
Table 4.2.39: Adductovarus 5th toe

Reporting exercise intolerance

Reporting exercise intolerance	Adductovarus 5th toes	
	Yes	No
Yes	35	15
No	12	11
Total	47	26

Figure 4.2.24 shows the relationship between adductovarus 5th toes and reporting exercise intolerance.

Figure 4.2.24: Adductovarus 5th toes



Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without adductovarus 5th toes (χ^2 = 2.183, p = 0.140).

4.2.4.3 Adductovarus 4th and 5th toes

Table 4.2.40 shows the number of patients with adductovarus 4th and 5th toes who reported leg pain.

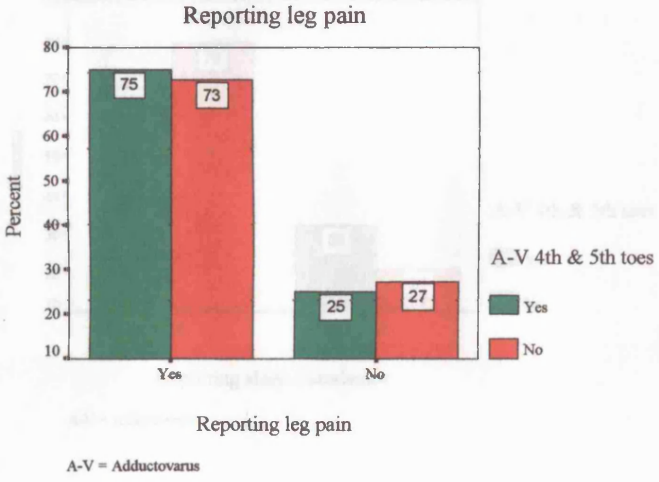
Table 4.2.40: Adductovarus 4th and 5th toes

Reporting leg pain

Reporting leg pain	Adductovarus 4th & 5th toes	
	Yes	No
Yes	21	18
No	7	6
Total	28	24

Figure 4.2.25 shows the relationship between adductovarus 4th and 5th toes and reporting leg pain.

Figure 4.2.25: Adductovarus 4th and 5th toes



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without adductovarus 4th and 5th toes (χ^2 = 0.000, p = 1.000).

Table 4.2.41 shows the number of patients with adductovarus 4th and 5th toes who reported sleep disturbance.

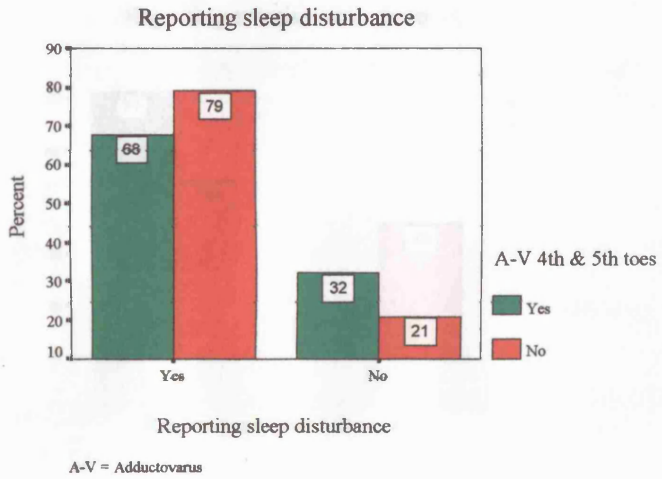
Table 4.2.41: Adductovarus 4th and 5th toes

Reporting sleep disturbance

Reporting sleep disturbance	Adductovarus 4th & 5th toes	
	Yes	No
Yes	19	19
No	9	5
Total	28	24

Figure 4.2.26 shows the relationship between adductovarus 4th and 5th toes and reporting sleep disturbance.

Figure 4.2.26: Adductovarus 4th and 5th toes



A-V = Adductovarus

Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without adductovarus 4th and 5th toes ($\chi^2 = 0.254$, $p = 0.614$).

Table 4.2.42 shows the number of patients with adductovarus 4th and 5th toes who reported exercise intolerance.

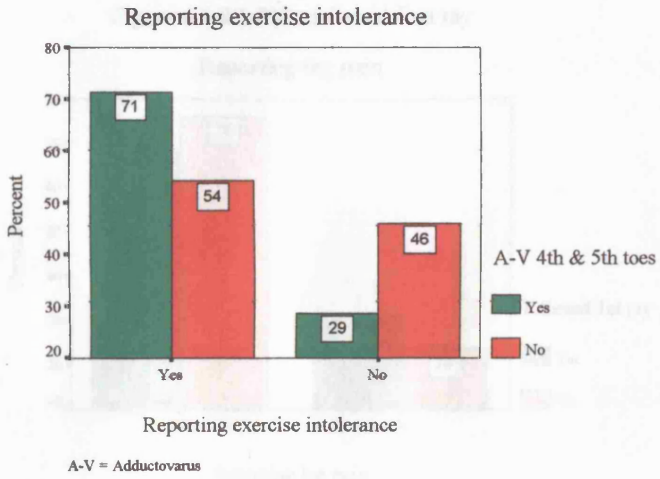
Table 4.2.42: Adductovarus 4th and 5th toes

Reporting exercise intolerance

Reporting exercise intolerance	Adductovarus 4th & 5th toes	
	Yes	No
Yes	20	13
No	8	11
Total	28	24

Figure 4.2.27 shows the relationship between adductovarus 4th and 5th toes and reporting exercise intolerance

Figure 4.2.27: Adductovarus 4th and 5th toes



A-V = Adductovarus

Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without adductovarus 4th and 5th toes ($\chi^2 = 1.661$, $p = 0.198$).

4.2.4.4 The 1st ray

Table 4.2.43 shows the number of patients with plantarflexed 1st ray who reported leg pain.

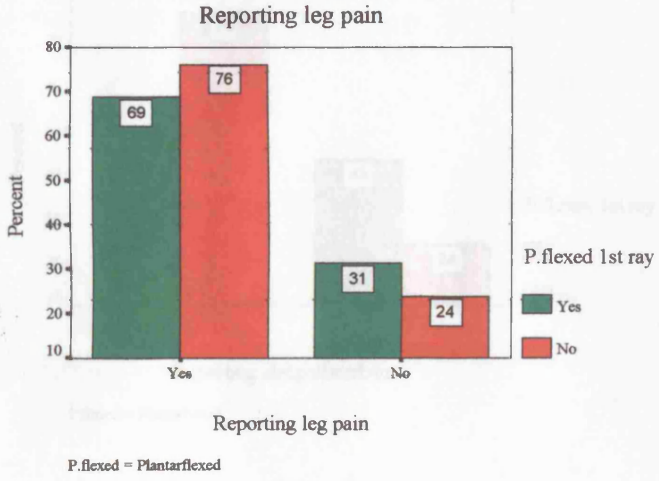
Table 4.2.43: Plantar flexed 1st ray

Reporting leg pain

Reporting leg pain	Plantarflexed 1st ray	
	Yes	No
Yes	11	48
No	5	15
Total	16	63

Figure 4.2.28 shows the relationship between plantarflexed 1st ray and reporting leg pain.

Figure 4.2.28: Plantarflexed first ray



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without plantarflexed first rays ($\chi^2 = 0.374$, $p = 0.541$).

Table 4.2.44 shows the number of patients with plantarflexed 1st ray who reported sleep disturbance.

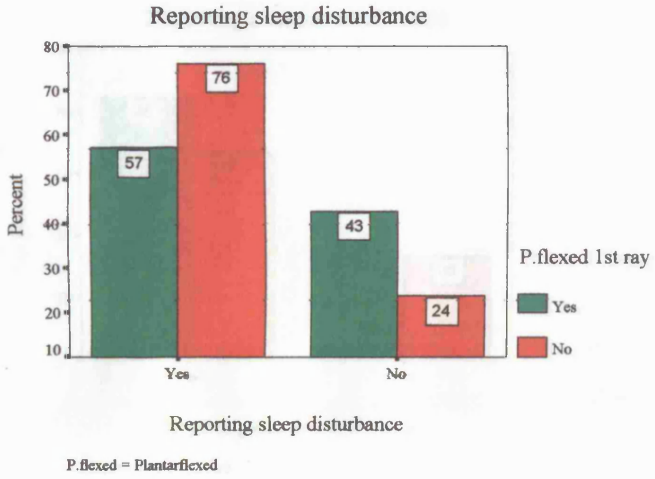
Table 4.2.44: Plantar flexed 1st ray

Reporting leg pain

Reporting sleep disturbance	Plantarflexed 1st ray	
	Yes	No
Yes	8	48
No	6	15
Total	14	63

Figure 4.2.29 shows the relationship between plantarflexed 1st ray and reporting leg pain.

Figure 4.2.29: Plantarflexed first ray



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without plantarflexed first rays (χ^2 = 2.095, p = 0.148).

Table 4.2.45 shows the number of patients with plantarflexed 1st ray who reported exercise intolerance.

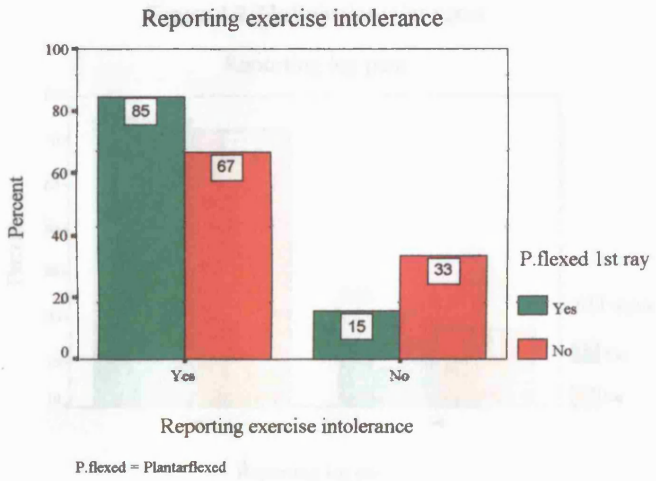
Table 4.2.45: Plantar flexed 1st ray

Reporting exercise intolerance

Reporting exercise intolerance	Plantarflexed 1st ray	
	Yes	No
Yes	11	42
No	2	21
Total	13	63

Figure 4.2.30 shows the relationship between plantarflexed 1st ray and reporting leg pain.

Figure 4.2.30: Plantarflexed first ray



P.flexed = Plantarflexed

Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without plantarflexed first rays (χ^2 = 1.645, p = 0.200), although low frequency of one variable renders such a result unreliable.

4.2.4.5 Subtalar joint varus

Table 4.2.46 shows the number of patients with subtalar joint varus who reported leg pain.

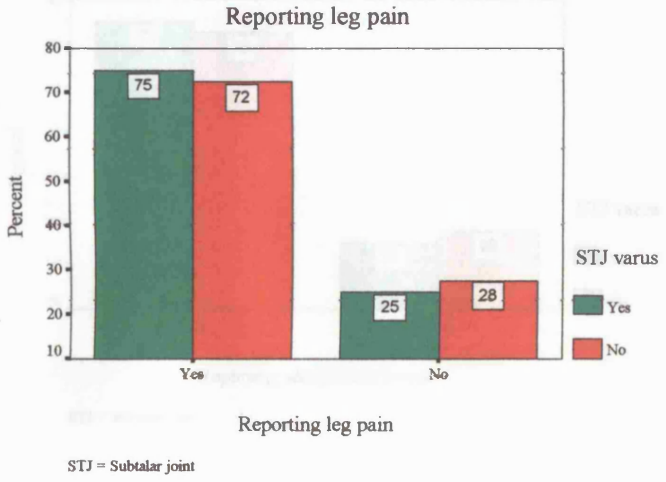
Table 4.2.46: Subtalar joint varus

Reporting leg pain

Reporting leg pain	Subtalar joint varus	
	Yes	No
Yes	12	42
No	4	16
Total	16	58

Figure 4.2.31 shows the relationship between subtalar joint varus and reporting leg pain.

Figure 4.2.31: Subtalar joint varus



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without subtalar joint varus ($\chi^2 = 0.043$, $p = 0.837$), although low frequency of one variable renders such a result unreliable.

Table 4.2.47 shows the number of patients with subtalar joint varus who reported sleep disturbance.

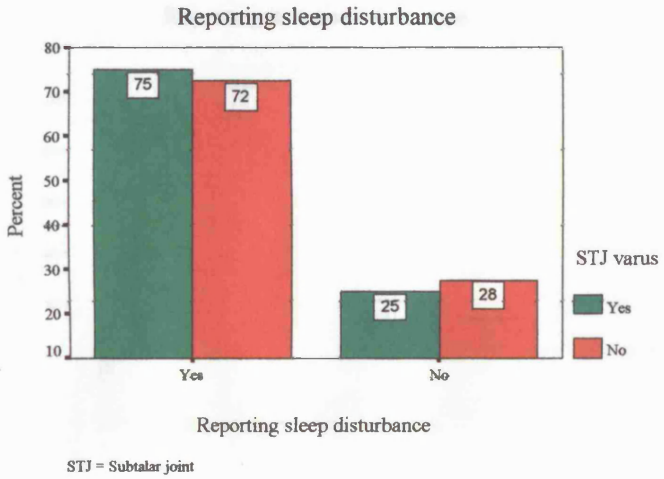
Table 4.2.47: Subtalar joint varus

Reporting sleep disturbance

Reporting sleep disturbance	Subtalar joint varus	
	Yes	No
Yes	12	42
No	4	16
Total	16	58

Figure 4.2.32 shows the relationship between subtalar joint varus and reporting sleep disturbance.

Figure 4.2.32: Subtalar joint varus



STJ = Subtalar joint

Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without subtalar joint varus (χ^2 = 0.043, p = 0.837), although low frequency of one variable renders such a result unreliable.

Table 4.2.48 shows the number of patients with subtalar joint varus who reported exercise intolerance.

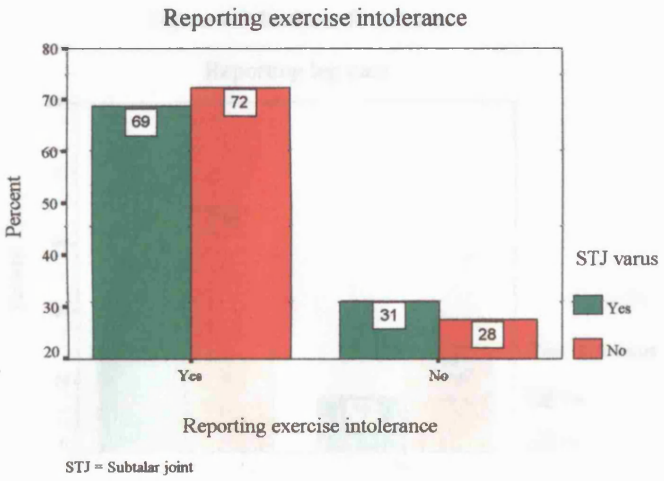
Table 4.2.48: Subtalar joint varus

Reporting exercise intolerance

Reporting exercise intolerance	Subtalar joint varus	
	Yes	No
Yes	11	42
No	5	16
Total	16	58

Figure 4.2.33 shows the relationship between subtalar joint varus and reporting exercise intolerance.

Figure 4.2.33: Subtalar joint varus



STJ = Subtalar joint

Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without subtalar joint varus (χ^2 = 0.083, p = 0.774).

4.2.4.6 Rear foot varus

Table 4.2.49 shows the number of patients with rear foot varus who reported leg pain.

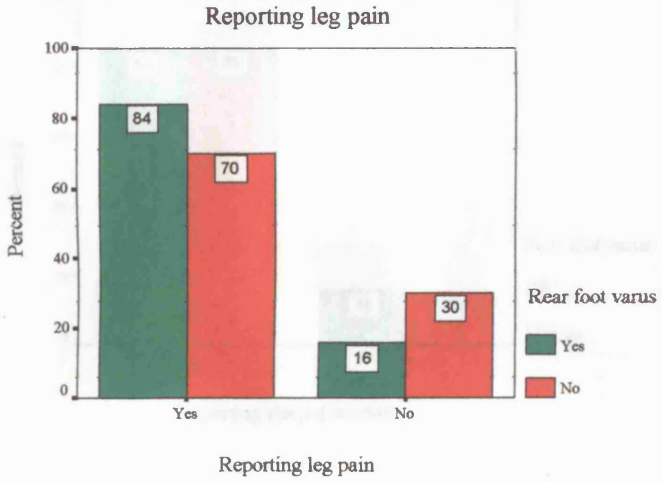
Table 4.2.49: Rear foot varus

Reporting leg pain

Reporting leg pain	Rear foot varus	
	Yes	No
Yes	16	35
No	3	15
Total	19	50

Figure 4.2.34 shows the relationship between rear foot varus and reporting leg pain.

Figure 4.2.34: Rear foot varus



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without rear foot varus ($\chi^2 = 1.442$, $p = 0.230$), although low frequency of one variable renders such a result invalid.

Table 4.2.50 shows the number of patients with rear foot varus who reported sleep disturbance.

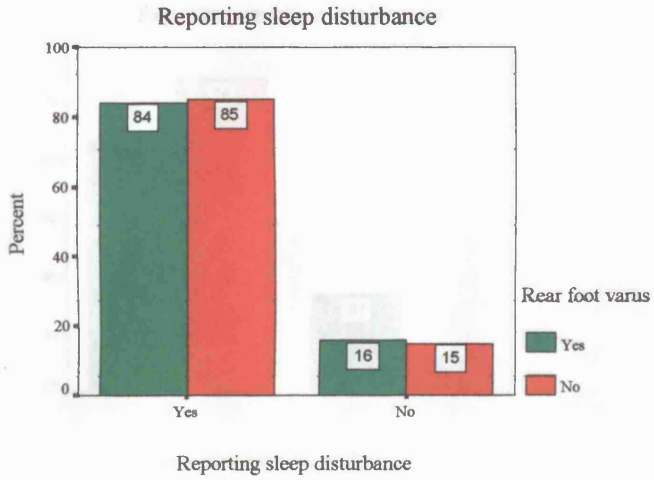
Table 4.2.50: Rear foot varus

Reporting sleep disturbance

Reporting sleep disturbance	Rear foot varus	
	Yes	No
Yes	16	34
No	3	16
Total	19	50

Figure 4.2.35 shows the relationship between rear foot varus and reporting sleep disturbance.

Figure 4.2.35: Rear foot varus



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without rear foot varus ($\chi^2 = 0.006$, $p = 0.937$), although low frequency of one variable renders such a result invalid.

Table 4.2.51 shows the number of patients with rear foot varus who reported exercise intolerance.

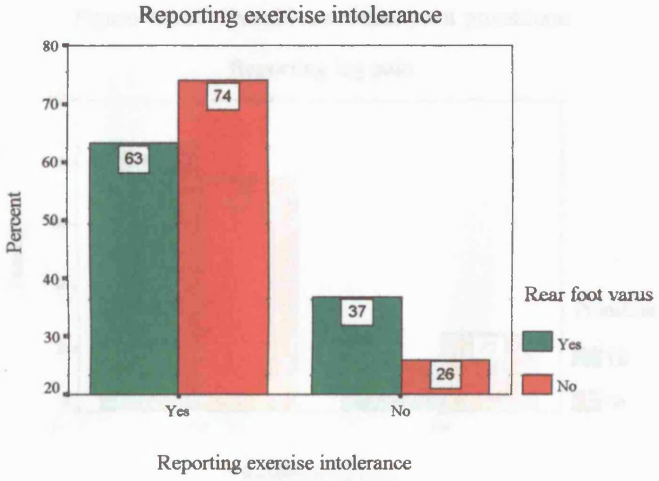
Table 4.2.51: Rear foot varus

Reporting exercise intolerance

Reporting exercise intolerance	Rear foot varus	
	Yes	No
Yes	11	42
No	5	16
Total	16	58

Figure 4.2.36 shows the relationship between subtalar joint varus and reporting exercise intolerance.

Figure 4.2.36: Rear foot varus



Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without rear foot varus (χ^2 = 0.083, p = 0.774).

4.2.4.7 Excessive subtalar joint pronation

Table 4.2.52 shows the number of patients with excessive subtalar joint pronation who reported leg pain.

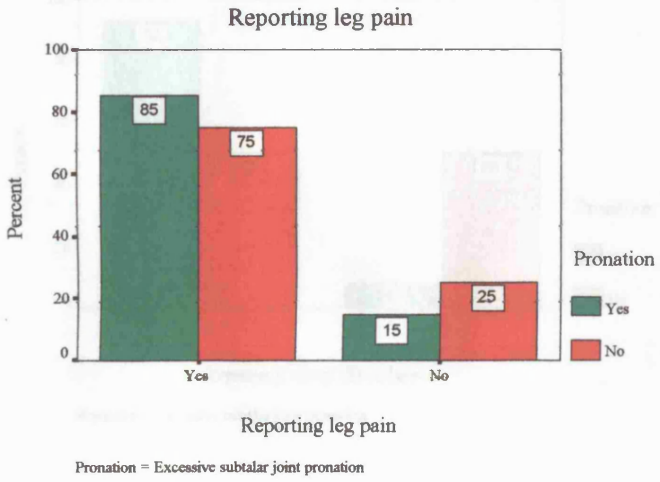
Table 4.2.52: Excessive subtalar joint pronation

Reporting leg pain

Reporting leg pain	Excessive subtalar joint pronation	
	Yes	No
Yes	47	9
No	18	3
Total	65	12

Figure 4.2.37 shows the relationship between excessive subtalar joint pronation and reporting leg pain.

Figure 4.2.37: Excessive subtalar joint pronationn



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without excessive subtalar joint pronation (χ^2 = 0.037, p = 0.847), although low frequency of one variable renders such a result invalid.

Table 4.2.53 shows the number of patients with excessive subtalar joint pronation who reported sleep disturbance.

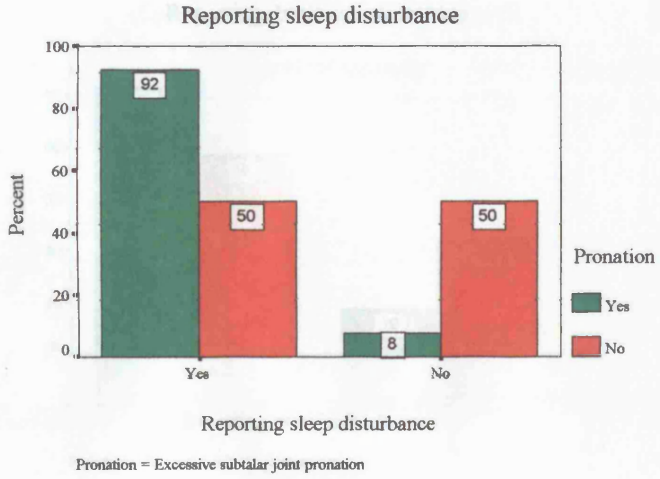
Table 4.2.53: Excessive subtalar joint pronation

Reporting sleep disturbance

Reporting sleep disturbance	Excessive subtalar joint pronation	
	Yes	No
Yes	49	6
No	14	6
Total	63	12

Figure 4.2.38 shows the relationship between excessive subtalar joint pronation and reporting sleep disturbance.

Figure 4.2.38: Excessive subtalar joint pronationn



Chi squared test showed that significantly more patients with excessive subtalar joint pronation than those without, reported sleep disturbance (χ^2 = 3.977, p = 0.046).

Table 4.2.54 shows the number of patients with excessive subtalar joint pronation who reported exercise intolerance.

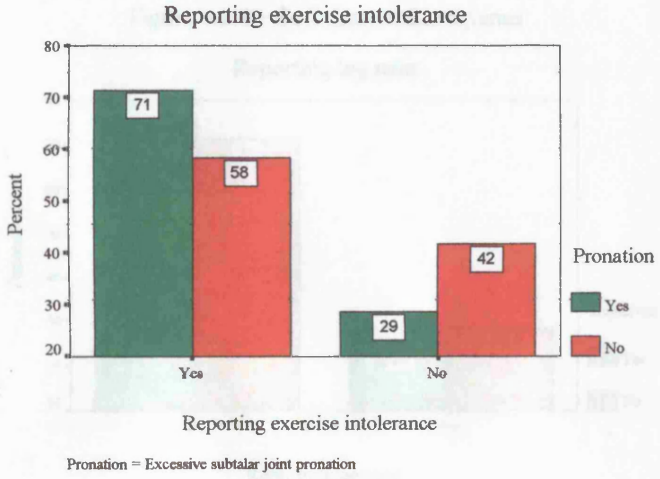
Table 4.2.54: Excessive subtalar joint pronation

Reporting exercise intolerance

Reporting exercise intolerance	Excessive subtalar joint pronation	
	Yes	No
Yes	45	7
No	18	5
Total	63	12

Figure 4.2.39 shows the relationship between excessive subtalar joint pronation and reporting exercise intolerance.

Figure 4.2.39: Excessive subtalar joint pronationn



Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without excessive subtalar joint pronation ($\chi^2 = 0.813$, $p = 0.367$).

4.2.4.8 Soft tissue ankle equinus

Table 4.2.55 shows the number of patients with soft tissue ankle equinus who reported leg pain.

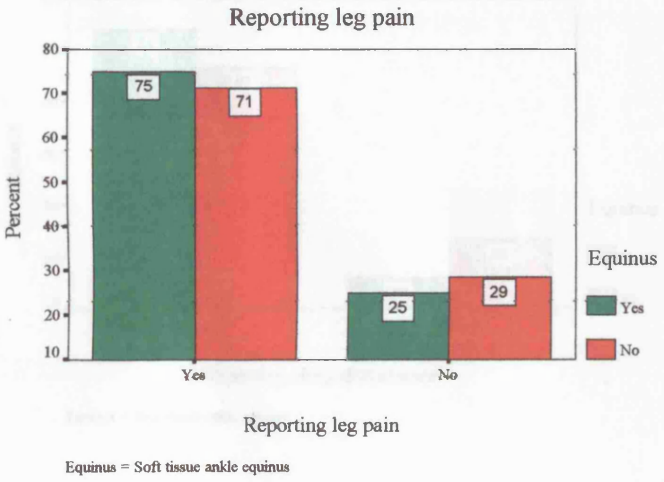
Table 4.2.55: Soft tissue ankle equinus

Reporting leg pain

Reporting leg pain	Soft tissue ankle equinus	
	Yes	No
Yes	45	15
No	15	6
Total	60	21

Figure 4.2.40 shows the relationship between soft tissue ankle equinus and reporting leg pain.

Figure 4.2.40: Soft tissue ankle equinus



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without soft tissue ankle equinus ($\chi^2 = 0.103$, $p = 0.748$).

Table 4.2.56 shows the number of patients with soft tissue ankle equinus who reported sleep disturbance.

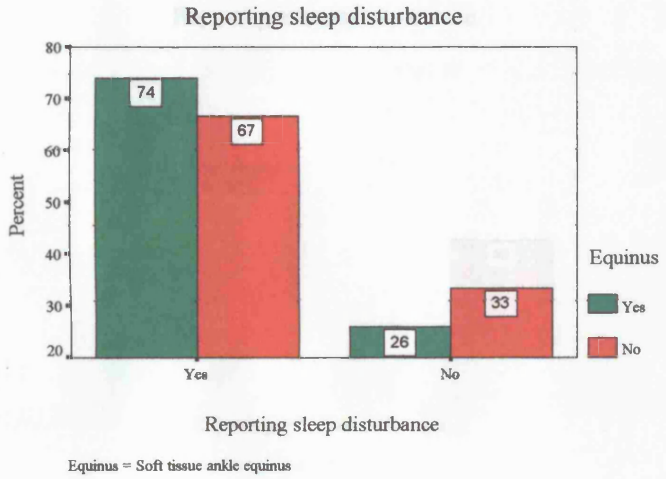
Table 4.2.56: Soft tissue ankle equinus

Reporting sleep disturbance

Reporting sleep disturbance	Soft tissue ankle equinus	
	Yes	No
Yes	43	14
No	15	7
Total	58	21

Figure 4.2.41 shows the relationship between soft tissue ankle equinus and reporting sleep disturbance.

Figure 4.2.41: Soft tissue ankle equinus



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without soft tissue ankle equinus ($\chi^2 = 0.428$, $p = 0.513$).

Table 4.2.57 shows the number of patients with soft tissue ankle equinus who reported exercise intolerance.

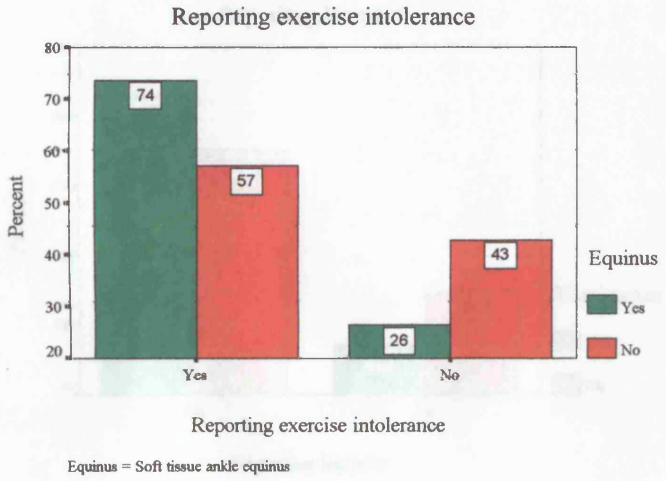
Table 4.2.57: Soft tissue ankle equinus

Reporting exercise intolerance

Reporting exercise intolerance	Soft tissue ankle equinus	
	Yes	No
Yes	42	12
No	15	9
Total	57	21

Figure 4.2.42 shows the relationship between soft tissue ankle equinus and reporting exercise intolerance.

Figure 4.2.42: Soft tissue ankle equinus



Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without soft tissue ankle equinus ($\chi^2 = 1.971$, $p = 0.160$).

4.2.4.9 Tibial varum

Table 4.2.58 shows the number of patients with tibial varum who reported leg pain.

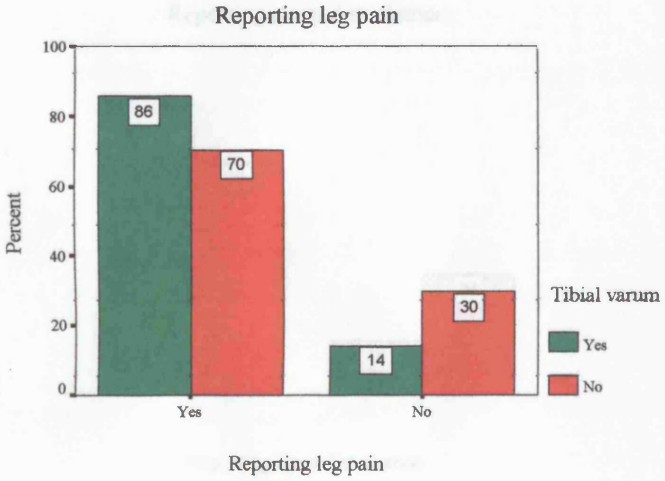
Table 4.2.58: Tibial varum

Reporting leg pain

Reporting leg pain	Tibial varum	
	Yes	No
Yes	18	31
No	3	13
Total	21	44

Figure 4.2.43 shows the relationship between tibial varum and reporting leg pain.

Figure 4.2.43: Tibial varum



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without tibial varum ($\chi^2 = 1.784$, $p = 0.182$), although low frequency of one variable renders such a result unreliable.

Table 4.2.59 shows the number of patients with tibial varum who reported sleep disturbance.

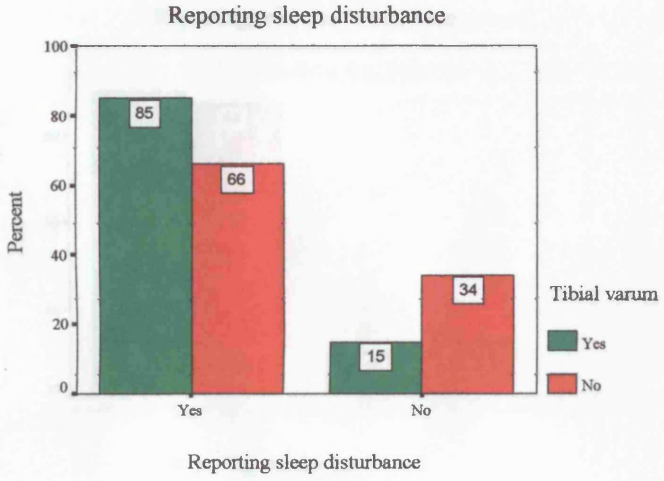
Table 4.2.59: Tibial varum

Reporting sleep disturbance

Reporting sleep disturbance	Tibial varum	
	Yes	No
Yes	17	29
No	3	15
Total	20	44

Figure 4.2.44 shows the relationship between tibial varum and reporting sleep disturbance.

Figure 4.2.44: Tibial varum



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without tibial varum ($\chi^2 = 2.479$, $p = 0.115$), although low frequency of one variable renders such a result unreliable.

Table 4.2.60 shows the number of patients with tibial varum who reported exercise intolerance.

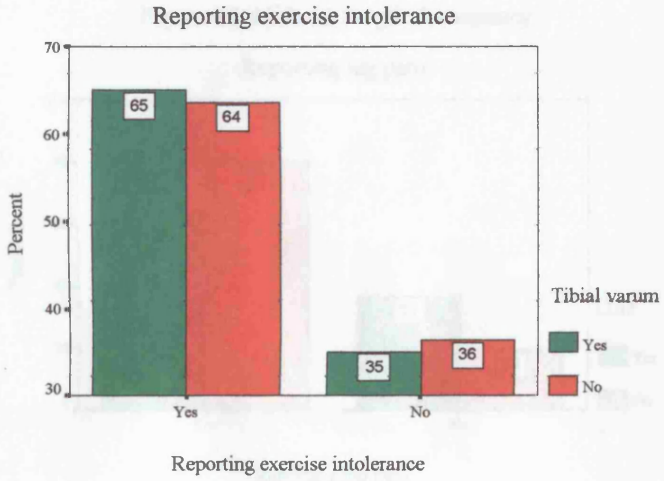
Table 4.2.60: Tibial varum

Reporting exercise intolerance

Reporting exercise intolerance	Tibial varum	
	Yes	No
Yes	13	28
No	7	16
Total	20	44

Figure 4.2.45 shows the relationship between tibial varum and reporting exercise intolerance.

Figure 4.2.45: Tibial varum



Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without tibial varum ($\chi^2 = 0.011$, p = 0.916).

4.2.4.10 Limb length discrepancy

Table 4.2.61 shows the number of patients with limb length discrepancy who reported leg pain.

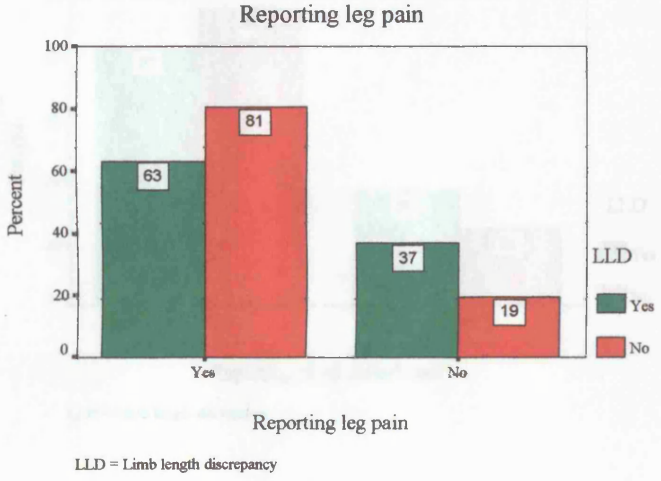
Table 4.2.61: Limb length discrepancy

Reporting leg pain

Reporting leg pain	Limb length discrepancy	
	Yes	No
Yes	12	29
No	1	7
Total	13	36

Figure 4.2.46 shows the relationship between limb length discrepancy and reporting leg pain.

Figure 4.2.46: Limb length discrepancy



LLD = Limb length discrepancy

Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without limb length discrepancy ($\chi^2 = 0.966$, p = 0.326), although low frequency of one variable renders such a result unreliable.

Table 4.2.62 shows the number of patients with limb length discrepancy who reported sleep disturbance.

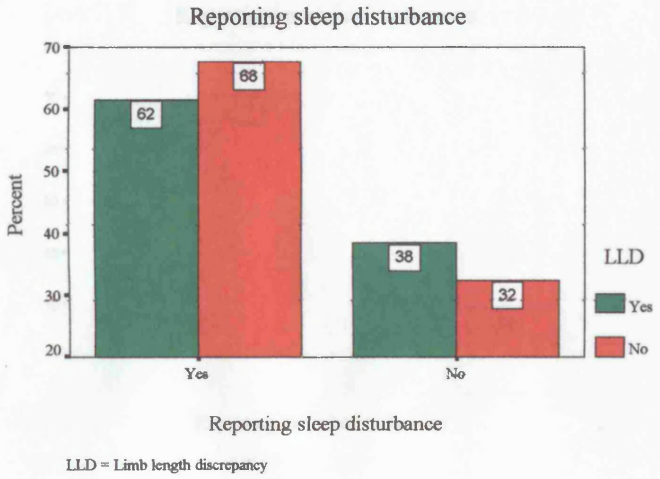
Table 4.2.62: Limb length discrepancy

Reporting sleep disturbance

Reporting sleep disturbance	Limb length discrepancy	
	Yes	No
Yes	8	23
No	5	11
Total	13	34

Figure 4.2.47 shows the relationship between limb length discrepancy and reporting sleep disturbance.

Figure 4.2.47: Limb length discrepancy



LLD = Limb length discrepancy

Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without limb length discrepancy ($\chi^2 = 0.156$, $p = 0.693$).

Table 4.2.63 shows the number of patients with limb length discrepancy who reported exercise intolerance.

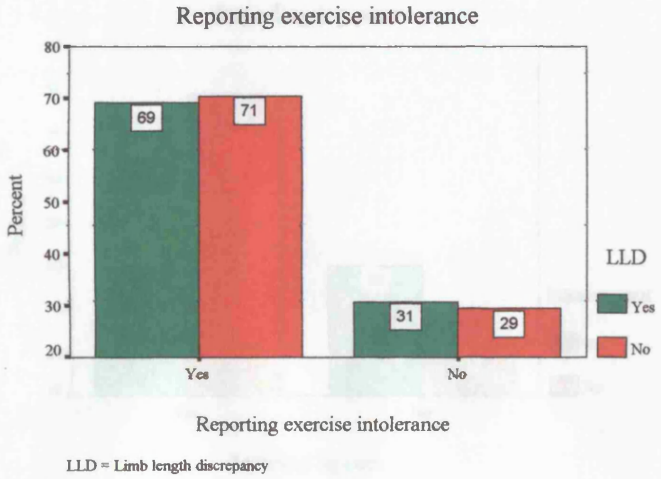
Table 4.2.63: Limb length discrepancy

Reporting exercise intolerance

Reporting exercise intolerance	Limb length discrepancy	
	Yes	No
Yes	9	24
No	4	10
Total	13	34

Figure 4.2.48 shows the relationship between limb length discrepancy and reporting exercise intolerance.

Figure 4.2.48: Limb length discrepancy



LLD = Limb length discrepancy

Chi squared test showed no significant difference in the prevalence of reporting exercise intolerance between patients with and without limb length discrepancy ($\chi^2 = 0.008$, $p = 0.927$).

4.2.4.11 Intoeing gait

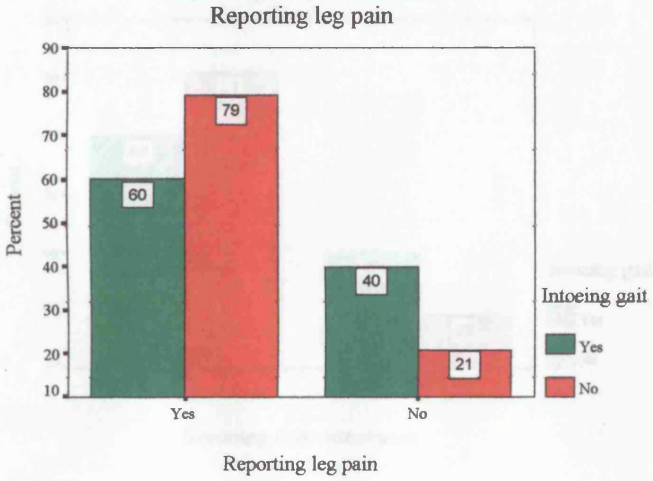
Table 4.2.64 shows the number of patients with intoeing gait who reported leg pain.

Table 4.2.64: Intoeing gait
Reporting leg pain

Reporting leg pain	Intoeing gait	
	Yes	No
Yes	6	38
No	4	10
Total	10	48

Figure 4.2.49 shows the relationship between intoeing gait and reporting leg pain.

Figure 4.2.49: Intoeing gait



Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without intoeing gait ($\chi^2 = 1.660$, $p = 0.198$), although low frequency of one variable renders such a result unreliable.

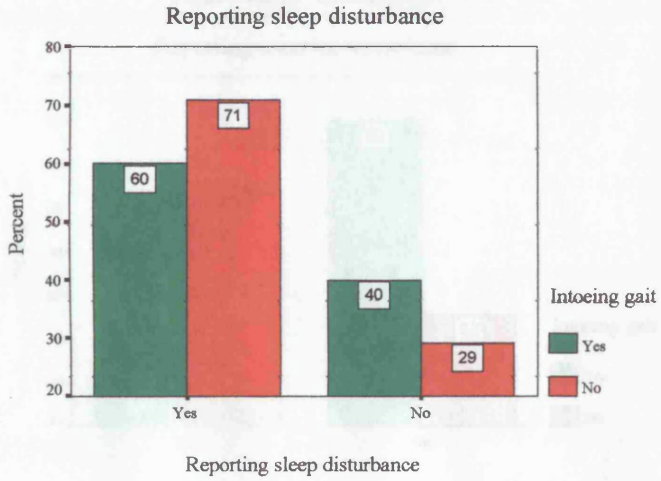
Table 4.2.65 shows the number of patients with intoeing gait who reported sleep disturbance.

Table 4.2.65: Intoeing gait

Reporting sleep disturbance	Intoeing gait	
	Yes	No
Yes	6	34
No	4	14
Total	10	48

Figure 4.2.50 shows the relationship between intoeing gait and reporting sleep disturbance.

Figure 4.2.50: Intoeing gait



Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without intoeing gait ($\chi^2 = 0.454$, $p = 0.501$), although low frequency of one variable renders such a result unreliable.

Table 4.2.66 shows the number of patients with intoeing gait who reported exercise intolerance.

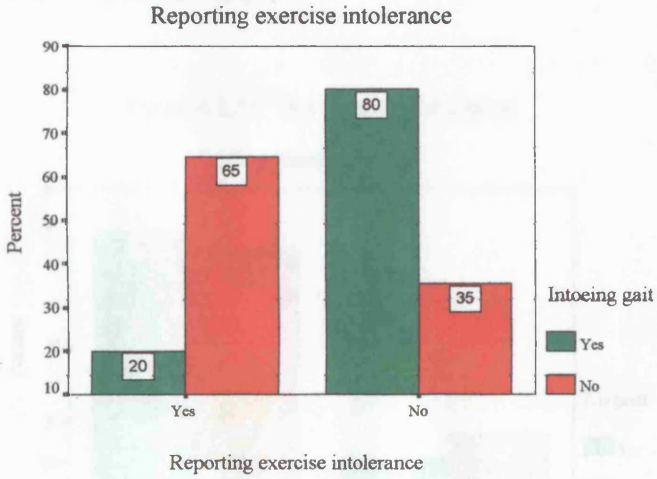
Table 4.2.66: Intoeing gait

Reporting exercise intolerance

Reporting exercise intolerance	Intoeing gait	
	Yes	No
Yes	2	31
No	8	17
Total	10	48

Figure 4.2.51 shows the relationship between intoeing gait and reporting exercise intolerance.

Figure 4.2.51: Intoeing gait



Chi squared test showed significantly more patients without intoeing gait than with, reported exercise intolerance (χ^2 = 6.707, p = 0.010) although low frequency of one variable renders such a result unreliable. Fisher's exact test accounted for the low frequency and showed a significant relationship (p = 0.014).

4.2.4.12 Anterior displacement of tibialis posterior tendon

Table 4.2.67 shows the number of patients with anteriorly displaced tibialis posterior tendon who reported leg pain.

Table 4.2.67: Anterior displacement of tibialis posterior tendon

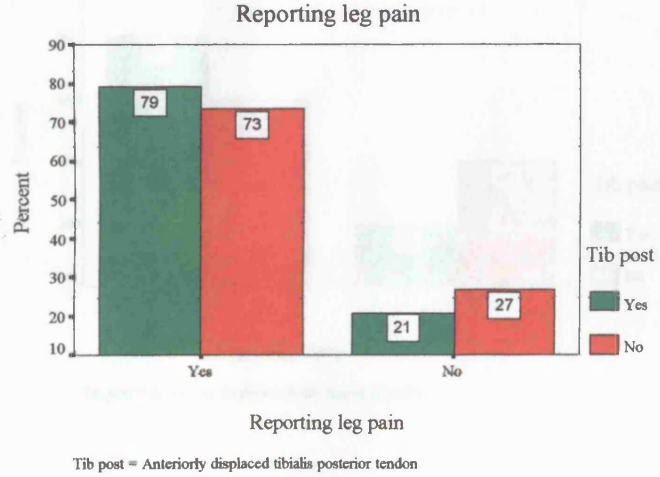
Reporting leg pain

Reporting leg pain	Ant tib post	
	Yes	No
Yes	34	11
No	9	4
Total	43	15

Ant tib post = Anterior displacement of tibialis posterior tendon

Figure 4.2.52 shows the relationship between anteriorly displaced tibialis posterior tendon and reporting leg pain.

Figure 4.2.52: Tibialis posterior tendon



Tib post = Anteriorly displaced tibialis posterior tendon

Chi squared test showed no significant difference in the prevalence of reporting leg pain between patients with and without anteriorly displaced tibialis posterior tendon ($\chi^2 = 0.210$, $p = 0.646$), although low frequency of one variable renders such a result unreliable.

Table 4.2.68 shows the number of patients with anteriorly displaced tibialis posterior tendon who reported sleep disturbance.

Table 4.2.68: Anterior displacement of tibialis posterior tendon

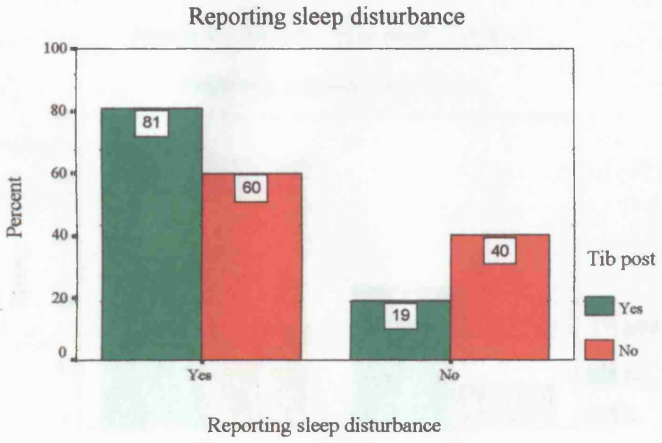
Reporting sleep disturbance

Reporting sleep disturbance	Ant tib post	
	Yes	No
Yes	34	9
No	8	6
Total	42	15

Ant tib post = Anterior displacement of tibialis posterior tendon

Figure 4.2.53 shows the relationship between anteriorly displaced tibialis posterior tendon and reporting sleep disturbance.

Figure 4.2.53: Tibialis posterior tendon



Tib post = Anteriorly displaced tibialis posterior tendon

Chi squared test showed no significant difference in the prevalence of reporting sleep disturbance between patients with and without anteriorly displaced tibialis posterior tendon ($\chi^2 = 2.619$, $p = 0.106$).

Table 4.2.69 shows the number of patients with anteriorly displaced tibialis posterior tendon who reported exercise intolerance.

Table 4.2.69: Anterior displacement of tibialis posterior tendon

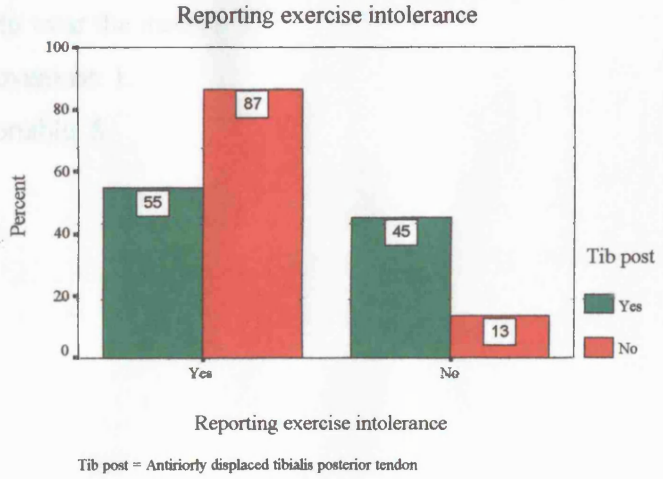
Reporting exercise intolerance

Reporting exercise intolerance	Ant tib post	
	Yes	No
Yes	23	13
No	19	2
Total	42	15

Ant tib post = Anterior displacement of tibialis posterior tendon

Figure 4.2.54 shows the relationship between anteriorly displaced tibialis posterior tendon and reporting exercise intolerance.

Figure 4.2.54: Tibialis posterior tendon



Tib post = Antiriorly displaced tibialis posterior tendon

Chi squared test showed that significantly more patients without anteriorly displaced tibialis posterior tendon than without reported exercise intolerance (χ^2 = 4.835, p = 0.028) although low frequency of one variable renders such a result unreliable. Fisher's exact test accounted for the low frequency and showed a significant relationship (p = 0.033)

4.2.5 Response to treatment

Feedback on response to treatment was received from 49 out of 84 patients (58.3%). All 49 respondents received simple insoles prescribed and manufactured by the same operator.

4.2.5.1 Duration of use

The duration of insole use varied between patients ranging from 0 to 208 weeks (Mean = 57.16, S.D. = 44.21).

4.2.5.2 Continuation of insole use

At the time of receipt of feedback forms, 19 patients were still using the insoles. 29 patients for various reasons discontinued the use of insoles:

- Pain disappeared: 2.
- Insoles worn out: 5.
- Shoe size changed: 9.
- Heart operation: 1.
- Refused to wear the insoles: 1.
- No improvement: 1.
- Uncomfortable: 8.

4.2.5.3 Comfort

Patients reported the degree of comfort of insoles on a scale of 1-3 where, 1 is very uncomfortable, 2 is comfortable and 3 is very comfortable.

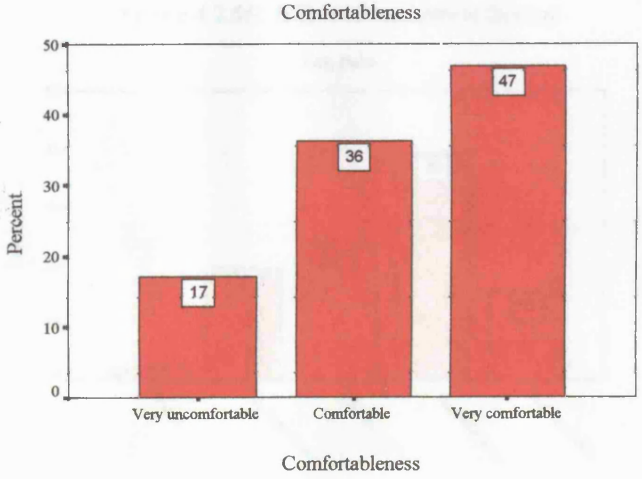
Table 4.2.70 shows the number of patients who reported the various degrees of comfortableness.

Table 4.2.70: Comfortableness

Degree	Patients
Very uncomfortable	8
Comfortable	17
Very comfortable	22
Total	47

Figure 4.2.55 shows the percentage of patients who reported each degree of comfortableness.

Figure 4.2.55: Effect of mechanical therapy



4.2.5.4 Effect on leg pain

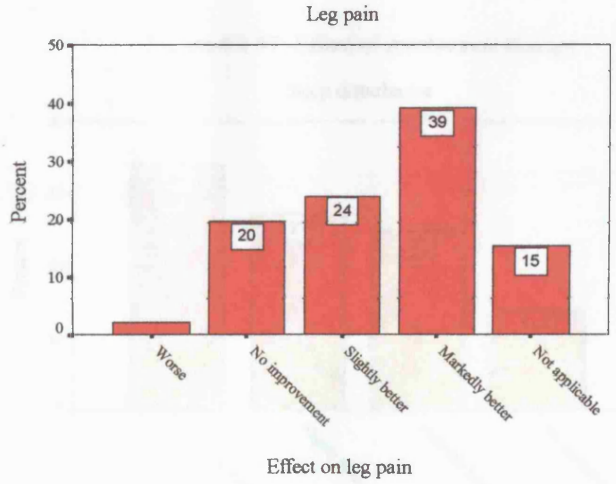
Table 4.2.71 shows the number of patients who reported the effect of the insole use on episodes of leg pain. The category "Not applicable" refers to patients who did not experience episodes of leg pain prior to insole use.

Table 4.2.71: Effect on leg pain

Degree	Patients
Markedly worse	0
Worse	1
No effect	9
Slightly better	11
Markedly better	18
Not applicable	7
Total	46

Figure 4.2.56 shows the percentage of patients who reported the various effects of mechanical therapy on episodes of leg pain.

Figure 4.2.56: Effect of mechanical therapy



4.2.5.5 Effect on Sleep disturbance

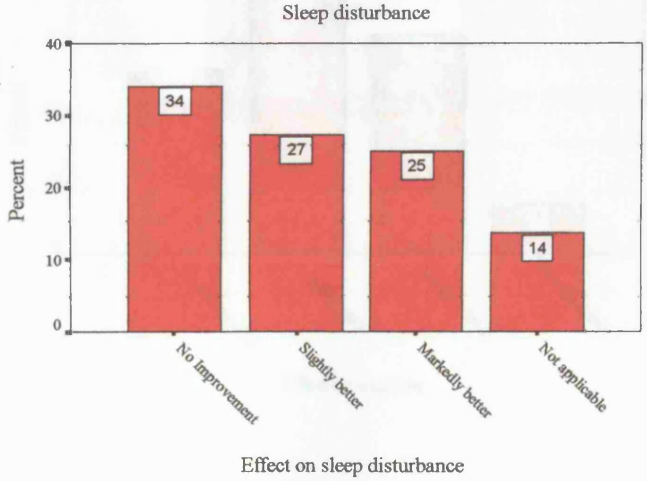
Table 4.2.72 shows the number of patients who reported the effect of the insole use on episodes of sleep disturbance. The category "Not applicable" refers to patients who did not experience episodes of sleep disturbance prior to insole use.

Table 4.2.72: Effect on sleep disturbance

Degree	Patients
Markedly worse	0
Worse	0
No effect	15
Slightly better	12
Markedly better	11
Not applicable	6
Total	44

Figure 4.2.57 shows the percentage of patients who reported the various effects of mechanical therapy on episodes of sleep disturbance.

Figure 4.2.57: Effect of mechanical therapy



4.2.5.6 Effect on exercise intolerance

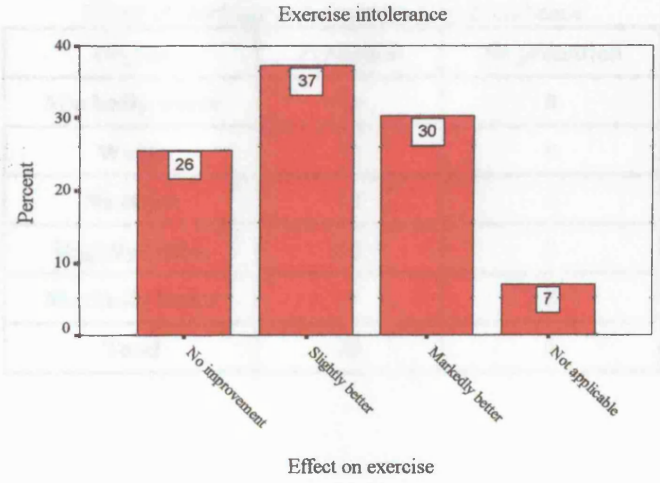
Table 4.2.73 shows the number of patients who reported the effect of the insole use on exercise intolerance. The category "Not applicable" refers to patients who did not experience exercise intolerance prior to insole use.

Table 4.2.73: Effect on exercise intolerance

Degree	Patients
Markedly worse	0
Worse	0
No effect	11
Slightly better	16
Markedly better	13
Not applicable	3
Total	43

Figure 4.2.58 shows the percentage of patients who reported the various effects of mechanical therapy on episodes of exercise intolerance.

Figure 4.2.58: Effect of mechanical therapy



4.2.5.7. Treatment in excessive subtalar joint pronation

Table 4.2.74 shows the effect of mechanical therapy on episodes of leg pain in patients with and without observed excessive subtalar joint pronation.

Table 4.2.74: Excessive subtalar joint pronation
Effect of mechanical therapy on leg pain

Degree	Pronation	No pronation
Markedly worse	0	0
Worse	1	0
No effect	5	2
Slightly better	11	0
Markedly better	14	3
Total	31	5

Table 4.2.75 shows the effect of mechanical therapy on episodes of sleep disturbance in patients with and without observed excessive subtalar joint pronation.

Table 4.2.75: Excessive subtalar joint pronation
Effect of mechanical therapy on sleep disturbance

Degree	Pronation	No pronation
Markedly worse	0	0
Worse	0	0
No effect	11	2
Slightly better	10	2
Markedly better	9	2
Total	30	6

Table 4.2.76 shows the effect of mechanical therapy on episodes of exercise intolerance in patients with and without observed excessive subtalar joint pronation.

Table 4.2.76: Excessive subtalar joint pronation

Effect of mechanical therapy on exercise intolerance

Degree	Pronation	No pronation
Markedly worse	0	0
Worse	0	0
No effect	5	4
Slightly better	15	0
Markedly better	11	2
Total	31	6

4.2.5.8. Treatment in soft tissue ankle equinus

Table 4.2.77 shows the effect of mechanical therapy on episodes of leg pain in patients with and without observed soft tissue ankle equinus.

Table 4.2.77: Soft tissue ankle equinus
Effect of mechanical therapy on leg pain

Degree	Equinus	No equinus
Markedly worse	0	0
Worse	1	0
No effect	7	4
Slightly better	6	4
Markedly better	15	5
Total	29	13

Table 4.2.78 shows the effect of mechanical therapy on episodes of sleep disturbance in patients with and without observed soft tissue ankle equinus.

Table 4.2.78: Soft tissue ankle equinus
Effect of mechanical therapy on sleep disturbance

Degree	Equinus	No equinus
Markedly worse	0	0
Worse	0	0
No effect	11	4
Slightly better	8	2
Markedly better	10	1
Total	29	7

Table 4.2.79 shows the effect of mechanical therapy on episodes of exercise intolerance in patients with and without observed soft tissue ankle equinus.

Table 4.2.79: Soft tissue ankle equinus

Effect of mechanical therapy on exercise intolerance

Degree	Equinus	No equinus
Markedly worse	**0**	**0**
Worse	**0**	**0**
No effect	**8**	**3**
Slightly better	**11**	**4**
Markedly better	**11**	**1**
Total	**30**	**8**

4.2.5.9. Treatment in anteriorly displaced tibialis posterior tendon

Table 4.2.80 shows the effect of mechanical therapy on episodes of leg pain in patients with and without observed anterior displacement of tibialis posterior tendon.

Table 4.2.80: Anterior displacement of tibialis posterior tendon

Effect of mechanical therapy on leg pain

Degree	Equinus	No equinus
Markedly worse	0	0
Worse	1	0
No effect	4	2
Slightly better	7	1
Markedly better	10	4
Total	22	7

Table 4.2.81 shows the effect of mechanical therapy on episodes of sleep disturbance in patients with and without observed anterior displacement of tibialis posterior tendon.

Table 4.2.81: Anterior displacement of tibialis posterior tendon

Effect of mechanical therapy on sleep disturbance

Degree	Equinus	No equinus
Markedly worse	0	0
Worse	0	0
No effect	7	2
Slightly better	8	2
Markedly better	7	2
Total	22	6

Table 4.2.82 shows the effect of mechanical therapy on episodes of exercise intolerance in patients with and without observed anterior displacement of tibialis posterior tendon.

Table 4.2.82: Anterior displacement of tibialis posterior tendon

Effect of mechanical therapy on exercise intolerance

Degree	Displaced	Not displaced
Markedly worse	**0**	**0**
Worse	**0**	**0**
No effect	**5**	**2**
Slightly better	**8**	**3**
Markedly better	**9**	**1**
Total	**22**	**6**

Chapter 5

Discussion

5.1. Leg pain Survey

5.1.1. Introduction

The primary aim of this study was to investigate the phenomenon of recurrent lower limb pain of unknown aetiology (PUA) in children with 22q11 deletion. Since general population data concerning this symptom in the literature are scarce and conflicting (section 2.2.2.5), it was essential to generate primary data in order to provide a comparison and to highlight any discrepancies between children with 22q11 deletion and children of the general population. While investigating this phenomenon has yielded a wealth of general population information, most of which could not be found in previous literature, such data are only secondary to this work and are mainly used to analyse and characterise this phenomenon in children with 22q11 deletion.

No previous studies that investigated PUA in children with 22q11 deletion were identified in the literature or on personal contact with a number of clinicians and researchers who frequently deal with such patients and families. The so called "growing pains" constituted the nearest clinical entity to what in this investigation is referred to as "recurrent lower limb pain of unknown aetiology". Previous studies have investigated this phenomenon in the general population only, but almost always assumed arbitrary and varying definitions of growing pains (Hawksley 1939) and used varying methodologies. Definitions used by previous studies involved some speculation of the characteristics of growing pains. Not surprisingly, this discrepancy of definition and methodology produced a wide variation of results that were often contradictory to one another. Such diversity did not further the understanding of growing pains and prevented data pooling for meta analysis.

In order to avoid this speculation pitfall, data were systematically gathered and analysed through the research process with no preconceived theory in mind but a theory was allowed to emerge from the data.

Theory derived from data is more likely to resemble the 'reality' than is theory derived by putting together a series of concepts based on experience or solely through speculation (Strauss & Corbin 1998). Such an approach is more likely to offer insight, enhance understanding, and provide a meaningful guide to action. Using such exploratory research strategy, this study was able to identify, for the first time, the most common characteristics of recurrent lower limb pain of unknown aetiology in children with 22q11 deletion and in children of the general population. Although personal experience was instrumental in identifying PUA, sleep disturbance and exercise intolerance as the symptoms to be investigated in this study, the characteristics of these symptoms were allowed to spontaneously emerge through the collected data with no speculative interference and with no prior preconceptions of such characteristics.

The questionnaire, criteria for selection and exclusion, method of administration, method of collection and analysis tools were applied identically to the patient and the general population groups. This allowed direct comparison of prevalence and characteristics of the investigated symptoms in both populations. As an exploratory method, it allowed the identification of the characteristics of the phenomena under investigation while avoiding personal speculation of such characteristics. It has also breached the gap created by the insufficiency of current literature.

The tem "Patients" refers to the sample of children with known 22q11 deletion, while the term "General population (Gp" or Gp subjects)" refers to the sample of school children representing members of the general population.

It is possible that the general population sample may contain children with 22q11 deletion. Such is the character of a random general population sample that it will contain subjects with abnormalities and others without. Exclusion of children with 22q11 deletion from the general population sample was not only impractical but would have also introduced an element of sample bias and would have breached the rules of random sampling. Additionally, with a documented prevalence of 22q11 deletion of 1:5000 (Scambler 1993) and a general population sample of 5211 subjects, only about one patient with 22q11 deletion is expected

to be included in the general population sample. Considering that a proportion of children with 22q11 deletion do not attend mainstream schools but need to attend special schools as a result of their learning difficulties and that completed questionnaires were received from only 1247 respondents, further decreases the likelihood that a significant number of children with 22q11 deletion will be included in the general population sample.

It is therefore worthy of note that comparisons are made between children with 22q11 deletion and members of the general population rather than specifically with children without a deletion on the 22nd chromosome.

Due to repeated reports of sleep disturbance and intolerance to physical exercise amongst patients with 22q11 deletion, the leg pain questionnaire distributed to patients and general population subjectss included inquiries about these two features. The aim was to investigate any association between these symptoms and PUA.

5.1.2. Discussion

5.1.2.1. Methodology

The leg pain survey estimated a prevalence of reporting leg pain of 57.14% among patients and 45.62% among Gp subjects. This prevalence difference proved to be statistically significant ($p < 0.05$).

The data were manipulated to exclude cases of leg pain due to a known aetiology, since such type of pain is inherently different than the type under investigation. Only recognised clinical entities were excluded. Exclusions included responses that reported the following conditions:

- Arthritis.
- Osgood Schlatter Disease.
- Accidental or surgical trauma.
- Chondromalacia patellae.
- Tendonitis.

Such conditions are expected to be diagnosed following appropriate medical examination and investigation or reported in response to a known injury or surgical operation and are well known causes of lower limb pain.

Other conditions that might be used as labels or tentative explanation of recurrent leg pain were not regarded as a firm aetiology for recurrent lower limb pain and were therefore not excluded. Such conditions included:

- Growing pains.
- Cold / damp weather.
- Sports / exercise.
- Ligamentous laxity
- Pronation.
- Cartilage.
- Tight muscles.

Such conditions may act as aggravating factors and are not necessarily the primary aetiology of leg pain.
This manipulation resulted in changing of prevalence to 56.77% in the patient group and to 40.63% in the Gp group. The statistical significance of this difference was elevated to $p = 0.001$.

The data were further manipulated by adding cases of leg pain due to a known aetiology to cases that reported no leg pain, creating the collective category of "Others". This data manipulation was aimed at isolating cases of PUA from all other cases. Cases of leg pain due to a known aetiology are therefore included within a category that is best described as cases that did not report PUA. This manoeuvre was necessary to provided an insight into the prevalence and characteristics of PUA without contamination by other types of leg pain that are not investigated in this study.

Subsequent data analysis therefore included two categories, Pain of Unknown Aetiology (PUA) and Others (O). The latter category comprised responses that reported no leg pain and responses that reported leg pain due to a known aetiology.

This further manipulation estimated a prevalence of PUA of 56.3% in the patient group and 37.17% in the Gp group. The statistical significance of this difference was further elevated to $p = 0.000$.

It is possible that some of the cases categorised as PUA should have in fact been included as pain due to a known aetiology e.g. cases that reported "Cartilage" as the aetiology of leg pain. These cases were categorised as such due to the uncertainty of the reported diagnosis. Only 1 patient and 23 Gp subjects reported conditions that could have been misinterpreted in this way and their placement as such, is not expected to significantly affect the outcome of statistical tests. Furthermore, exclusion of such cases on grounds of doubtful reporting without adding them to the category of no pain, would still have kept a statistically significant relationship ($p = 0.001$).

Previous studies estimated a prevalence of growing pains in the general population that widely varied between 2.4% to 50% (Al-Khattat and Campbell 2000). Due to the considerable methodological differences it is difficult to compare the results of this work with the results of previous studies.

5.1.2.2. Symptom prevalences

Data analysis showed that significantly more patients than Gp subjects reported recurrent lower limb pain of unknown aetiology (PUA), sleep disturbance and exercise intolerance. Whether or not an association can be demonstrated between these symptoms, this significant difference in their prevalence may indicate that the genetic abnormality associated with 22q11 deletion is responsible for the significantly higher prevalence in children with 22q11 deletion compared with children of the general population. Alternatively, one or more of the effects of that deletion may cause the higher prevalence in children with 22q11 deletion. As an analogy, central cyanosis is a known consequence of congenital heart disease. Central cyanosis in a patient with 22q11 deletion is not thought to result from the genetic abnormality but is caused by the congenital heart disease resulting from such an abnormality.

It follows that if these symptoms were not the direct result of the chromosomal abnormality, the significant difference in their prevalence between the patient and the Gp groups may be due to a difference in aetiological factors or a difference in the magnitude of similar aetiological factors. Psychological factors, for example, may differ between the two populations or may be similar but more severe in one population than the other. It is beyond the scope of this work to attempt to identify causal factors, but the results appear to suggest the presence of differences in the type or the magnitude of the underlying cause between the patient and the Gp groups. Alternatively, the stimulus responsible for generating the symptom in patients and Gp subjects may be similar or even identical but the significant difference in its prevalence is resulting from differences in stimulus perception between individuals of the two populations.

5.1.2.3. Effect of age

During analysis of the effect of age on PUA, sleep disturbance and exercise intolerance, age categories were combined to avoid low frequencies in narrower age ranges and to ensure validity of Chi squared tests. Three age categories were therefore statistically analysed: 2-7, 8-11 and 12-20 years old. The creation of these age categories was based purely on the suitability of their frequencies to undergo statistical tests. A possible deficiency in this work may be that no account was taken of the possible biological effects of the various ages on PUA, sleep disturbance and exercise intolerance and it would have been ideal for the statistical analysis to include narrower age ranges. Frequency distributions across the various age categories prevented this luxury but trends shown in corresponding graphs within the results section support the statistical findings of this study in the wider age ranges although similar findings within narrower age ranges can not be statistically verified.

Previous authors suggested various ages of onset and peak for growing pains in children of the general population (Naish and Apley 1951, Brenning 1960, Sherry 1990). It is not clear how these were deduced and the possibility remains that the available evidence was not sufficient for their substantiation.

The results of this study appear to agree with some of the findings of previous studies and disagree with others. The work of Naish and Apley (1951) suggested that the age of onset of growing pain was between 8-12 years old, which is in rough agreement with this study, although the age of 8-11 emerges in this research as a peak age range rather than an age of onset, since it shows that 20% of all those with PUA were within the 2-7 years age category (Figure 4.1.6, section 4.1.3.3.).

Brenning (1960) reported a prevalence of growing pain of 13.6% in the 6-7 years age category and 19.8% in the 10-11 years age category. This is much lower than those found in this work which were 31% and 46% respectively (Figure 4.1.7, section 4.1.3.3.).

Sherry (1990) suggested that growing pains start between the ages of 3 and 5 years. In contrast, this study shows that only 5% of children of the general

population, who reported PUA, were between the ages of 2 and 5 years. This percentage progressively increases to 15% at the 6-7 years age category, peaks to 22% at the 8-9 years age category, decreases to 17% at the 10-11 years age category before increasing again to 22% at the 12-13 years age category (Figure 4.1.6, section 4.1.3.3.). This shows a general increase in the prevalence of PUA with advancing age and suggests that the majority of cases of PUA start after the age of 5 years.

In order to investigate an age of onset, a longitudinal study that examines a group of subjects over a period of time is required. It does not appear that the findings of Naish and Apley (1951) or Sherry (1990) were based on such a type of study and it is therefore difficult to agree with their suggestions regarding the age of onset for growing pain.

Both the patient and the Gp groups showed that significantly more children between the ages of 8-11 years reported PUA than children between the ages of 2-7 years. In addition, the Gp group showed that significantly more children between the ages of 12-20 years reported PUA than children between the ages of 2-7 years. This latter difference could not be seen in the patient group. This finding suggests a monophasic peak of PUA in patients with 22q11 deletion in contrast to a biphasic peak in children of the general population.

Figures 4.1.4 and 4.1.6 (section 4.1.3.3.) support such trends in narrower age ranges spanning 2 years at a time, although figure 4.1.4 shows what may be the beginning of a later peak in patients, starting at the 16-20 years age category. This later peak however cannot be verified from the available data.

It appears therefore that there is a peak age for PUA between 8-9 years in both patients with 22q11 deletions and in children of the general population. There is also a second peak in children of the general population at the age of 12-13.

It is possible that the peaking of reports of PUA at 8-9 years may be due to lack of reporting an existing pain in the younger age group of 2-7 years resulting from failure of recognising or articulating pain which in fact had been present for some

time. This is more likely in children with 22q11 deletion due to their communication disorder and difficulty with understanding abstract concepts, possibly including pain.

MacNish (1834) described sleep as an intermediate state between wakefulness and death; wakefulness being the active physical and intellectual state of all the animal, and death as that of their total suspension. This description of sleep is perhaps one of the first attempts to breach the boundary of regarding sleep as a passive process. Hobson (1989) claimed that more has been learned about sleep in the previous 60 years than in the preceding 6000. He maintains that sleep is not simply the absence of waking but is a dynamic behaviour, controlled by elaborate and precise mechanisms.

In 1990, the International Classification of Sleep Disorders (ICSD) was published to replace earlier classifications of sleep disorders that were symptom based. There are no large epidemiological studies on sleep disorders that are based on the new ICSD classification (Partinen 1994). No studies were identified that examined the prevalence of sleep disturbance specifically in children and adolescents. Previous studies of recurrent frequent insomnia in subjects between the ages of 15-94 years suggested a prevalence that varied between 2%-23.1% (Patinen & Rimpelä 1982, Lugaresi et al 1983, Kronholm & Hyppä 1985, Urponen et al 1988, Hyppä & Kronholm 1989).

Data analysis from this research showed an overall prevalence of sleep disturbance of 13% of general population children and adolescents between the ages of 2-20 years. As a result of the new classification of sleep disturbance and the varying methodology of previous studies, it is difficult to analyse the results of this work within the context of previous studies. The prevalence of sleep disturbance suggested by this study however appears to be in the middle of the range of prevalence suggested by previous work.

This work shows that significantly more patients experience sleep disturbance than Gp subjects in all the three statistically tested age categories. Figures 4.1.16 and 4.1.18 (section 4.1.4.3.) support this trend in narrower age ranges although

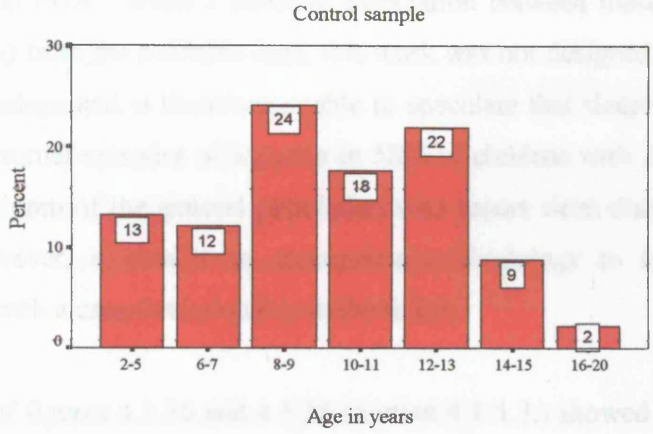
statistical significance cannot be tested due to low frequencies in some narrower age ranges.

Examination of figure 4.1.15 (Section 4.1.4.3.) showed that 6-7 years old is the peak age for sleep disturbance in children with 22q11 deletion. Figure 4.1.17 (Section 4.1.4.3.), on the other hand, showed a biphasic distribution for sleep disturbance in children of the general population with peaks at the ages of 8-9 and 12-13 years old.

It is interesting to observe that, in the general population the peak ages for sleep disturbance matched the peak ages for PUA (Figure 4.1.6, section 4.1.3.3.) with almost identical proportions, although only 56% of Gp subjects who reported sleep disturbance also experienced PUA. The monophasic peak for PUA in children with 22q11 deletion however was 8-9 years (Figure 4.1.4, section 4.1.3.3.) while that of sleep disturbance was 6-7 years (Figure 4.1.15, section 4.1.4.3). This difference may be due to the lack of reporting of PUA by patients in the younger age group of 6-7 years.

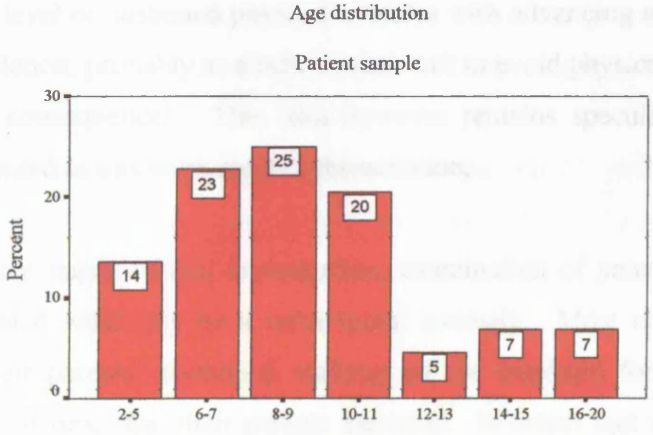
It appears therefore that an association exists between sleep disturbance and PUA in 56% of children and adolescents of the general population who report sleep disturbance. Figure 5.1 shows that the age distribution of children and adolescents of the general population who report both sleep disturbance and PUA, resembles the biphasic distribution of age for PUA (Figure 4.1.6, Section 4.1.3.3) and sleep disturbance (Figure 4.1.17, section 4.1.4.3).

Figure 5.1: Association of Sleep disturbance and PUA



Similarly, within the patient group 58% of patients who reported sleep disturbance also experienced PUA, although figure 5.2 shows that the peak age of this group resembled that of PUA (Figure 4.1.4, section 4.1.3.3) but was different from that of sleep disturbance (Figure 4.1.15, section 4.1.4.3).

Figure 5.2: Association of sleep disturbance and PUA



It appears therefore that a similar proportion of children with 22q11 deletion and children of the general population exhibit an association between sleep disturbance and PUA. While a possible association between these two features can be reported from the available data, this work was not designed to investigate causal relationships and is therefore unable to speculate that sleep disturbance is caused by nocturnal episodes of leg pain in 58% of children with 22q11 deletion or 56% of children of the general population who report sleep disturbance. It is important however, to design an appropriate methodology to investigate the possibility of such a causal relationship in the future.

Examination of figures 4.1.36 and 4.1.38 (section 4.1.4.3.) showed that 8-9 years is the peak age for exercise intolerance in children with 22q11 deletion while 12-13 years is the peak age for exercise intolerance in children of the general population. It also appears that exercise intolerance affects children with 22q11 deletion mostly at the earlier age of 2-9 years where as the majority of Gp subjects reporting exercise intolerance are at the later age group of 12-15 years. This later peaking of the prevalence of exercise intolerance in children of the general population may be related to a difference in the level of sustained physical activity between the two groups. If this were the case, that would suggest a decline in the level of sustained physical exercise with advancing age in children with 22q11 deletion, probably as a behavioural trait to avoid physical exercise due to its painful consequences. This idea however remains speculative, with no evidence presented in this work for its substantiation.

During the early stages of this investigation, examination of patients' gait on a treadmill revealed what may be a behavioural anomaly. Most children, to the surprise of their parents, continued walking on the treadmill for considerably longer periods of time than their parents expected. In actual fact many children stopped walking on the treadmill under protest as they would have liked to continue for longer. Also some children participated in physical exercises like dancing classes on regular basis with no problems during the exercise although they reported leg pain or showed features suggestive of leg pain during short walks. This phenomenon suggests a major psychological contribution to leg pain

associated with physical exercise and casts a doubt on the notion that such pain is purely of organic origin.

Of the 82 patients who reported exercise intolerance, 51 (62%) experienced PUA. Also of the 73 Gp subjects who reported exercise intolerance, 43 (59%) reported PUA. Similar to sleep disturbance, there appears to be an association between exercise intolerance and PUA in the majority of patients and Gp subjects who report exercise intolerance although a causal relationship can not be suggested by this work.

The line graphs shown in figures 5.3, 5.4 and 5.5 below compare the age prevalence of each of the three symptoms under investigation in the patient and the Gp groups. These graphs consolidate the findings discussed earlier and at the same time raise a number of interesting questions.

The behaviour of the line representing the patient group (red line) is one of early peak and later decline. The trough of this line lies very clearly at the age of 12-13 years in all the 3 symptoms. The age of 12-13 years in patients with 22q11 deletion therefore pauses an important question; What happens to children with 22q11 deletion at the age of 12-13 years old, that causes the prevalence of PUA, sleep disturbance and intolerance to physical exercise to drop to its lowest level?

More importantly, what happens to patients with 22q11 deletion in early childhood that they experience the highest prevalence of PUA, sleep disturbance and exercise intolerance?

Figure 5.3: PUA in the various age categories

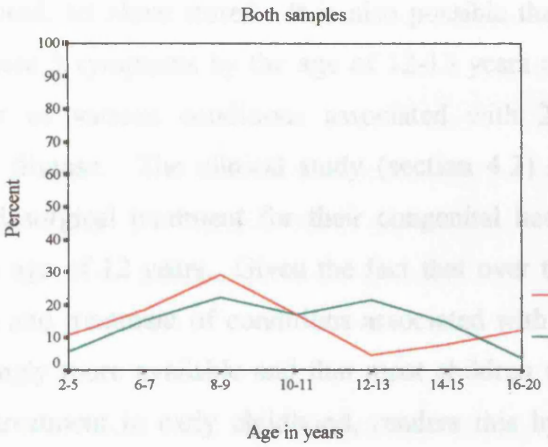


Figure 5.4: Sleep disturbance in the various age categories

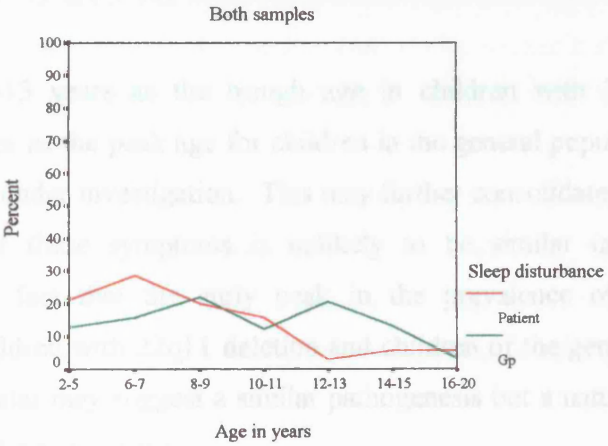
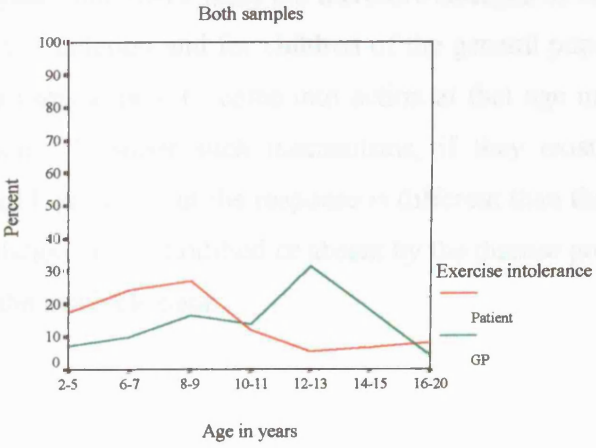


Figure 5.5: Exercise intolerance in the various age categories



A hypothesis of development of adaptive mechanisms, behavioural or otherwise, may answer the first question but such a hypotheses has certainly not been previously proposed, let alone tested. It is also possible that the decline in the prevalence of these 3 symptoms by the age of 12-13 years may be the result of earlier treatment of various conditions associated with 22q11 deletion e.g. congenital heart disease. The clinical study (section 4.2) shows that 60% of patients received surgical treatment for their congenital heart disease, 77% of those before the age of 12 years. Given the fact that over the last two decades earlier diagnosis and treatment of conditions associated with 22q11 deletion has become increasingly more available and that most children with 22q11 deletion receive such a treatment in early childhood, renders this hypotheses plausible. Such therapeutic interventions are obviously lacking in children of the general population.

The age of 12-13 years as the trough age in children with 22q11 deletion curiously emerges as the peak age for children in the general population in all the three symptoms under investigation. This may further consolidate the notion that the aetiology of these symptoms is unlikely to be similar in both groups. Conversely, the fact that the early peak in the prevalence of all the three symptoms in children with 22q11 deletion and children of the general population is somewhat similar may suggest a similar pathogenesis but a natural history that differs between the two groups.

The ages of 8-9 years and 12-13 years old therefore emerged as landmark ages for children with 22q11 deletion and for children of the general population. Natural biological mechanisms appear to come into action at that age in children of the general population. Weather such mechanisms, if they exist, also occur in children with 22q11 deletion but the response is different than that of children of the general population or are modified or absent by the disease process can not be speculated from the available data.

5.1.2.4. Effect of gender

Wall (1994) criticised what he called "a subculture of flippant and sexist pseudo explanation" that ignored the combination of the liability of women to certain painful conditions in contrast with their universal longer life expectancy. He summarised the experimental evidence on pain gender difference as horrible confusion due to failure to take into account the meaning of the noxious stimulus to the subject, the situation, the familiarity of the stimulus to the subject, the sex and the social status of the observers and the presence of peers who set approved standards of response.

He also expressed his doubt on what he called "the common myth that the difference is explained by hormones". Although he excluded migraine from this doubt, he went on to claim that female hormones might only have an exaggerating effect on what is basically a similar mechanism of migraine in both genders. His alternate hypothesis was that migraine might be a sex-linked condition.

Although many epidemiological reports highlighted differences in pain prevalence between females and males (e.g. Crook et al 1984, Sterenberg 1986, Brattberg et al 1989), it appears that caution must be exercised when interpreting the results of these surveys and it would be sometime before the question of pain gender difference is resolved.

No significant difference between females and males was demonstrated with PUA, sleep disturbance or exercise intolerance by this study in either the patient or the Gp group. Øster and Nielsen (1972) on the other hand reported a higher prevalence of growing pains in females compared with males although they did not test the statistical significance of this prevalence difference. It appears therefore that genetic, biological, psychological and environmental differences between the two genders play no part in the pathogenesis of PUA, sleep disturbance or exercise intolerance in children with 22q11 deletion or in children of the general population or that any such differences operate in opposing directions to give a null total effect.

5.1.2.5. Site of pain

Within the 22q11 deletion group there were 73 (18.7%) reports of pain in the knee and ankle with 317 (81.28%) reports of no pain in these sites (It should be borne in mind that each respondent may experience pain in more than one site). Similarly, within the Gp group there were 518 (18.83%) reports of pain in the knee or ankle with 2232 (81.16%) reports of no pain in these sites.

This suggests that in the majority of cases in both the patient and the Gp groups, PUA is not generally experienced in the knee or ankle regions. Pain in the knee and the ankle does not necessarily indicate articular involvement and such pain may arise extra-articularly with no joint pathology. It is not clear if previous studies that defined growing pain as "pain that does not involve the joints" (Hawksley 1938, Naish and Apley 1951, Øster and Nielson 1972, Abu-Arafeh and Russel 1996) diagnosed joint pathology using appropriate clinical and radiological techniques. This casts a doubt on the results of previous studies and their definition of growing pains should be viewed with caution.

Data analysis showed that significantly more Gp subjects than patients experienced PUA affecting the knee area. Whether such pain in children of the general population is articular or peri-articular, it may imply overuse as a result of more ability to exercise than children with 22q11 deletion. It may also be due to biomechanical foot abnormalities that may cause knee pain with exercise (Kelvin 1988).

Data analysis also showed that significantly more patients than Gp subjects experienced PUA affecting all other sites within the lower limb, including the ankle region. The most common site of pain in children with 22q11 deletion is below the back of the knee (calf muscle region). Oberkalaid et al (1997) also reported the calf area as the most common site of growing pain. Calf pain is more commonly linked to muscle fatigue and vascular events e.g. deep venous thrombosis and limb ischaemia. There is no evidence that 22q11 deletion predisposes to deep venous thrombosis. Cardiovascular abnormalities however are some of the most common features of 22q11 deletion. Such abnormalities do not only affect large organs like the heart or the great vessels but also commonly

affect relatively smaller circulatory systems like the carotid arteries. It is possible that functional or structural muscular microcirculatory abnormalities may be responsible for the recurrent episodes of PUA experienced by children with 22q11 deletion. No studies that investigated the micro vascular structure or function in the skeletal muscles of subjects with 22q11 deletion were identified in the literature and it would be useful if the results of such studies were available to confirm or refute such a possibility.

5.1.2.6. Clinical picture of PUA and sleep disturbance

No previous studies that investigated the frequency of episodes of PUA or sleep disturbance in children with 22q11 deletion or in children of the general population were identified. Although Abu-Arafeh and Russel (1996) defined "Recurrent limb pain of unknown aetiology" as "...at least two episodes of limb pain over a one year period", this definition appears to be arbitrary and derived from the authors' personal experience rather than being based on analysis of empirical data. This study did not investigate the frequency of leg pain episodes but used an arbitrary frequency as a criterion for selection. Furthermore, figure 4.1.10 (section 4.1.3.6) shows that the majority of children of the general population experience considerably more frequent episodes of PUA than Abu-Arafeh and Russel suggested.

Section 4.1.3.6 shows that in children and adolescents of the general population, episodes of PUA recur daily in 11%, weekly in 32% and less frequently in 57%. Section 4.1.4.5 shows that episodes of sleep disturbance in this group recur daily in 28%, weekly in 43% and less frequently in 29%. This appears to be the first work that reports the distribution of frequency of episodes of recurrent lower limb pain of unknown aetiology and recurrent episodes of sleep disturbance in children and adolescents of the general population on the basis of analysis of empirical data. It would have been very useful to compare these results with the results of similar studies. While this is not feasible due to the absence of such data in the literature, future studies may use this work for comparison and for further development of their own methodologies.

Further data analysis revealed that of the 18 patients who reported daily episodes of PUA, 7 (38%) experienced daily episodes of sleep disturbance. However, of the 50 Gp subjects who reported daily episodes of PUA, only 2 (4%) experienced daily episodes of sleep disturbance. This showed that significantly more patients than Gp subjects who experienced daily episodes of PUA also experienced daily episodes of sleep disturbance ($\chi^2 = 14.029$, $p = 0.000$). Although these findings do not indicate that sleep disturbance may be caused by leg pain in children with 22q11 deletion, there is a greater association between PUA and sleep disturbance in patients than in Gp subjects.

The Venn diagrams in figure 5.6 and 5.7 represent the population of patients and Gp subjects who exhibit one or more of the symptoms of PUA, sleep disturbance and exercise intolerance. They show the percentage of all patients and Gp subjects who exhibited various symptom combinations.

The diagrams clearly show that the majority of children with 22q11 deletion (79%) exhibit a combination of more than one symptom. Conversely, the majority of children of the general population (77%) exhibit only one symptom. This may further consolidate the suggestion that the underlying aetiology of these symptoms may differ between the two populations. It also raises a question as to a possible common pathogenesis of these three symptoms in children with 22q11 deletion.

Figure 5.6: Symptom combination in children with 22q11 deletion (n = 106)

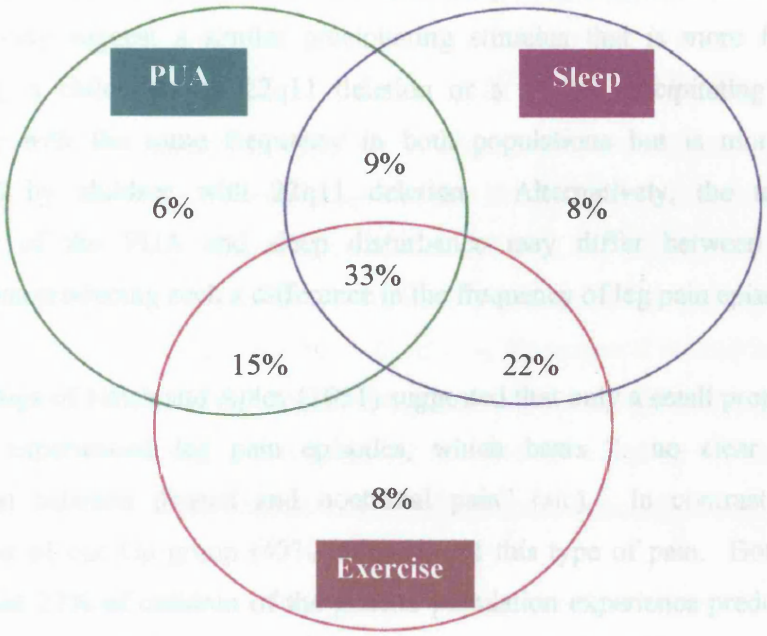
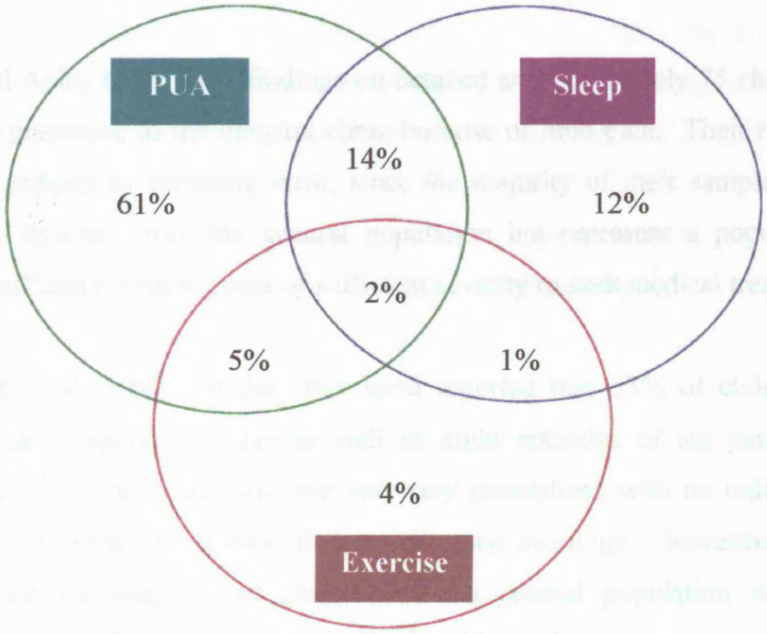


Figure 5.7: Symptom combination in children of the general population (n = 558)



Sections 4.1.3.6 and 4.1.4.5 show that significantly more patients than Gp subjects experience daily episodes of PUA and sleep disturbance. The difference in the frequency of episodes of PUA and sleep disturbance between the two samples may suggest a similar precipitating stimulus that is more frequently occurring in children with 22q11 deletion or a similar precipitating stimulus occurring with the same frequency in both populations but is more readily perceived by children with 22q11 deletion. Alternatively, the underlying aetiology of the PUA and sleep disturbance may differ between the two populations producing such a difference in the frequency of leg pain episodes.

The findings of Naish and Apley (1951) suggested that only a small proportion of children experienced leg pain episodes, which bears "...no clear clear-cut distinction between diurnal and nocturnal pain" (*sic*). In contrast, a large proportion of our Gp group (43%) experienced this type of pain. Both studies agreed that 27% of children of the general population experience predominantly nocturnal pain episodes. However, the finding of Naish and Apley (1951) that 64% of their sample experienced predominantly diurnal leg pain episodes is contradicted by our finding of only 30%.

Naish and Apley based their findings on detailed analysis of only 75 children, 45 of whom presented to the hospital clinic because of limb pain. Their results are therefore subject to sampling error, since the majority of their sample was not randomly selected from the general population but represent a population of children suffering from leg pain of sufficient severity to seek medical treatment.

Oberklaid et al (1997) on the other hand reported that 53% of children with growing pain experienced day as well as night episodes of leg pain. Their definition of growing pain however was very generalised with no indication of exclusion of cases of leg pain due to a known aetiology. Nevertheless, our finding that the majority of children of the general population with PUA experiencing variable day and night episode of leg pain is in agreement with the finding of Oberklaid et al (1997).

Figure 4.1.11 (section 4.1.3.7.) shows that more patients experience nocturnal and variable circadian episodes of PUA than Gp subjects while more Gp subjects experience diurnal episodes of PUA than patients, although this was not statistically significant. One reason for this observation may be that some children with 22q11 deletion experience delayed effect following daytime physical activities producing nocturnal episodes of leg pain. The statement of many parents within the clinical study supports this. Within the clinical study, many parents of children with 22q11 deletion claimed that they were more likely to experience nocturnal episodes of PUA if they performed more physical activity during the day. This phenomenon could not be investigated in children of the general population since the clinical study only included children with 22q11 deletion. The effect of daytime physical activities in children of the general population may not be subject to such a perception delay, producing diurnal episodes of leg pain.

Again, this is pure speculation and even if proves true, it would only be applicable to a small proportion of children with 22q11 deletion, since although nocturnal episodes of PUA occur in 34% of children with 22q11 deletion, 27% of children of the general population also experience nocturnal PUA. Assuming such a delay is responsible for the higher percentage of patients experiencing nocturnal leg pain episodes, this may be due to a more profound distractive effect of the activity exercised at the time.

Personal contact with many families revealed a repeated suggestion of high pain threshold for children with 22q11 deletion. The commonly used example was that children often ignore what appears to be a troublesome trauma, especially during engagement in entertaining activities, like playing. This high threshold for pain may be a result of distraction. This also supports the hypothesis of a delayed effect of painful stimuli in children with 22q11 deletion. Future research using quantitative sensory testing with and without distraction may be useful in this context.

Although there appear to be differences in the timing of leg pain episodes between the patient and the Gp groups as seen in figure 4.1.11 (section 4.1.3.7.),

these are not statistically significant. The statistically verifiable findings of this study (section 4.1.3.7) therefore, suggest that episodes of PUA mostly follow a variable circadian time pattern in both children with 22q11 deletion and in the general population.

No previous studies were identified that investigated the duration of leg pain episodes in children of the general population although Abu-Arafeh and Russel (1996) defined "Recurrent limb pain of unknown aetiology" as pain episodes lasting no more than 72 hours. Again, this appears to be an arbitrary criterion of selection rather than an empirically supported trend. Furthermore, our study shows that only 6% of the Gp group experienced episodes of leg pain lasting more than 12 hours. Data analysis showed that significantly more patients than Gp subjects experienced episodes of PUA lasting for less than one hour while significantly more Gp subjects experienced PUA lasting 3-6 hours. These findings suggest that children with 22q11 deletion experience episodes of PUA of shorter duration than Gp subjects.

This difference in the duration of episodes of PUA between the patient and the Gp groups may imply a difference in the underlying aetiology or in the magnitude of its effect. Alternatively, a difference in the adaptive mechanisms to pain may operate to produce such a difference in the duration of PUA between the two groups. It is possible that a delayed effect of a pain stimulus in children, with 22q11 deletion with or without an abnormally fast adaptive pain mechanism, may produce a delayed onset of pain perception together with a pain episode of a shorter duration.

This speculative context of the duration and frequency of leg pain episodes, may explain the frequent, short duration episodes of PUA experienced by children with 22q11 deletion compared with the less frequent, longer duration episodes of PUA experienced by children of the general population.

Only Naish and Apley (1951) referred briefly to severity of growing pain in one of their 3 clinical groups when they claimed that the pain was severe and of short

duration if it occurs diurnally in a patient who usually experience nocturnal pain episodes.

Our study showed that significantly more Gp subjects described their PUA as moderate while significantly more patients were not able to rate the severity of their PUA. Enquiries about pain severity will always yield subjective responses. Due to the communication disorder and difficulty with abstract concepts commonly experienced by children with 22q11 deletion, possibly including pain, such responses may prove difficult to collectively quantify a particular type of pain within the patient group. They may be useful however in quantifying response to treatment within each patient. This may also explain why significantly more patients than Gp subjects were unable to rate the severity of PUA. It is also possible that parents rather than patients may have completed some or all of leg pain questionnaire. While responses regarding frequency, timing and duration of episodes of PUA may be observed and reported by a third party, it is impossible for a third party to directly report the severity of pain experienced by a patient. At most, a third party may be able to hazard a guess as to the degree of distress experienced by a patient during what may be perceived as an episode of pain or may relay a subjective report.

Any attempt to draw conclusions from such a difference in pain severity between the two populations is therefore subject to possible error. It is interesting however to note that 19-20% of each group reported mild pain and 18-19% reported severe pain (Figure 4.1.13, section 4.1.3.9.) with no demonstrable significant difference between the two groups in the prevalence of reporting mild and severe pain.

It appears therefore that the majority of children with 22q11 deletion and the majority of children of the general population experience moderate PUA. Also around one fifth of each group experience mild PUA and another one fifth experience severe PUA.

5.1.2.7. Features suggestive of leg pain

Features suggestive of leg pain during episodes of sleep disturbance and exercise intolerance were examined as it was postulated that children with 22q11 deletion

might not report episodes of PUA. Behaviours that may be correlates of pain perception were therefore investigated

Data were examined to determine the proportion of patients and Gp subjects that reported leg pain during episodes of sleep disturbance. It was found that 52% of patients and 60% of Gp subjects reported leg pain during episodes of sleep disturbance. While this large percentage does not necessarily suggest a causal relationship, it suggests that episodes of sleep disturbance may be associated with episodes of leg pain in the majority of the patients and Gp subjects. Although proportionately more Gp subjects than patients reported leg pain during episodes of sleep disturbance, this relationship was not found to be statistically significant.

Examination of pain correlates during episodes of sleep disturbance showed that significantly more patients than Gp subjects cried during such episodes without reporting leg pain. On its own, this pain correlate is not enough to support a hypothesis of lack of reporting existing pain in children with 22q11 deletion, especially that crying does not only indicate physical pain but may result from distress caused by many stimuli, pain being only one of them.

Examination of pain correlates during episodes of exercise intolerance on the other hand, showed that significantly more patients than Gp subjects demanded to be picked up and cried during exercise without reporting leg pain. This combined with significantly more Gp subjects than patients reporting leg pain during exercise, diminishes the support for the hypothesis of lack of reporting an existing pain in patients with 22q11 deletion.

5.2. The clinical study

5.2.1. Introduction

The aim of this clinical study was to document lower limb biomechanical abnormalities in patients with a known 22q11 deletion, to look for any association between such abnormalities with symptoms reported by patients with 22q11 deletion and to report the effect of mechanical therapy of any diagnosed abnormalities on patients' symptoms.

The choice of the biomechanical lower limb abnormalities to observe and the types of clinical tests applied were based on the results of a preliminary study (Al-Khattat 1997, unpublished data) and were influenced by clinical practice in diagnosing such abnormalities within a U.K. National Health Service based community clinic. Such a choice was therefore influenced by the time and equipment available within such a setting. This study therefore aims to provide preliminary evidence of the nature of biomechanical lower limb abnormalities and the efficacy of mechanical therapy on lower limb and associated symptoms experienced by patients with 2211 deletion.

The findings of the preliminary study into leg pain in 22q11 deletion (Al-Khattat 1997, unpublished data) appears to be accepted within the 22q11 deletion community. This is evident from the addition of the symptom of "chronic leg pain" to the list of recognised clinical features of VCFS published by the VCFS Educational Foundation, New York, following the presentation of the results of the preliminary study before the Foundation's annual meetings. It is also evident from many inquiries regarding this symptom made by GPs and community and hospital paediatricians and from granting special needs status by social services to VCFS children with leg pain following reports of the findings of this study in individual patients. Still, treatment of lower limb symptoms of patients with 22q11 deletion remains only available within this research project. It is hoped that the evidence provided by this study will enable all patients with 22q11 deletion to receive treatment within their local medical services.

This clinical study has shown that the percentage of patients with 22q11 deletion who reported PUA, sleep disturbance and exercise intolerance was 72%, 73% and 70% respectively. These percentages are higher than those found during the analysis of the results of the questionnaire survey (56%, 64% and 69% respectively). Since the clinical study includes more patients with leg pain, unlike a random general population sample, it is subject to a sampling error similar to that of Naish and Apley (1951) (section 5.1.2). These percentages therefore cannot be generalised to the whole population of patients with 22q11 deletion.

5.2.2. Clinical examination

Clinical examination of patients followed a standard battery of observations that were systematically applied to each patient by the same clinician. This revealed the biomechanical lower limb abnormalities listed in table 5.2.1.

Table 5.2.1: Biomechanical lower limb abnormalities
Patients with 22q11 deletion (n = 84)

Abnormality	Percent
Excessive subtalar joint pronation	84%
Soft tissue ankle equinus	73%
Adductovarus 5th toes	60%
Anteriorly displaced tibialis posterior tendon	57%
Adductovarus 4th toes	37%
Limb length discrepancy	31%
Rear foot varus	28%
Tibial varum	27%
Subtalar joint varus	22%
Plantarflexed 1st ray	18%
Intoeing gait	17%
Tibial valgum	16%
Dorsiflexed 2nd toe	13%
Adductovarus 3rd toes	13%

A literature search revealed no previous work on the prevalence of these biomechanical abnormalities in the normal population. It is therefore not possible to report biomechanical abnormalities prevalence difference between children with 22q11 deletion and children of the general population. It is possible that the ongoing debate about the validity of clinical tests and measurement tools within the practice of podiatry may have been contributing to the lack of large epidemiological studies on biomechanical abnormalities of the lower limbs. It is important to bypass such an obstacle and to consider that a constant error within an observational tool will still yield valuable epidemiological data and will show general population trends.

The high percentage of biomechanical abnormalities demonstrated in this clinical study may not be representative of the population of children with 22q11 deletion in general since the used sample was not random but opportunistic. These results may however be more representative of the population of children with 22q11 deletion who experience PUA, sleep disturbance and exercise intolerance.

Data was analysed to investigate possible association between symptom reporting and biomechanical abnormalities. Contrary to expectation, almost all diagnosed biomechanical abnormalities did not seem to increase the chances of symptom reporting since nearly equal percentages of those with and without each biomechanical abnormality reported leg pain, sleep disturbance and exercise intolerance. Chi squared significance testing (section 4.2.4) confirmed the lack of a significant relationship between almost all diagnosed biomechanical abnormalities and symptom reporting. It is important however to realise that the very small number of patients who reported symptoms but showed no biomechanical abnormalities included in this study is likely to render statistical tests too insensitive to detect true associations.

The exception to that was that significantly more patients with excessive subtalar joint pronation than without reported sleep disturbance although there were no significant differences in reporting leg pain or exercise intolerance. It appears therefore that excessive subtalar joint pronation may somehow interfere with the sleep of children with 22q11 deletion. This idea however is not supported by

analysis of the effect of mechanical therapy on the episodes of sleep disturbance of patients with excessive subtalar joint pronation (section 4.2.5.7). This shows that sleep disturbance has improved by similar percentages in patients with and without excessive subtalar joint pronation in response to mechanical therapy. However, the small number of patients without excessive subtalar joint pronation who showed improvement in sleep disturbance in response to mechanical therapy renders statistical tests insensitive in demonstrating true significance. Whether excessive subtalar joint pronation causes muscle aching due to overuse or causes inefficient muscle oxygen consumption or any other yet to be proposed pathogenesis, is beyond the scope of this work.

Data analysis showed that the majority of respondents reported either slight or marked improvement of their symptoms in response to mechanical therapy yet, symptomatic patients with and without biomechanical foot abnormalities reported similar improvement (sections 4.2.5.7-4.2.5.9). This casts a doubt on the idea that mechanical therapy exerts its therapeutic effect by altering the position of the foot joins in stance and gait. It follows that symptoms that are thought to result from abnormal position of foot joints may in fact result from other unknown factors. Although this concept emerged through examination of patients with 22q11 deletion, future studies may wish to test it in subjects within a general population sample to provide evidence of the mechanisms of therapeutic actions of mechanical therapy.

Originally, diaries to document episodes of leg pain, sleep disturbance and exercise intolerance (appendix VIII) before and after the commencement of mechanical therapy were designed and administered to each family in order to test the effect of mechanical therapy on patients' symptoms. Only one family completed the diary. It is likely that the sustained regular observation and documentation required to complete these diaries was the reason for the poor response. A feedback form (appendix VI) that requires a one off completion was therefore designed and posted to all patients who received mechanical therapy. Completed feedback forms were received from 49 (58.3%) patients.

The majority of patients treated with mechanical therapy reported improvement in leg pain, sleep disturbance and exercise intolerance (sections 4.2.5.4-4.2.5.6). Whether or not a placebo effect is responsible for such an improvement, it appears appropriate to recommend a trial of mechanical therapy in patients with 22q11 deletion who experience PUA, sleep disturbance or exercise intolerance. Similar to the results of this clinical study, such treatment may improve these symptoms in at least a proportion of patients.

There is no doubt as to the importance of recognising the mechanism of action of any therapeutic measure. It is unwise however to refrain from using a known beneficial therapy just because its mechanism of action is unknown.

Chapter VI

Conclusions and recommendations

6.1. Conclusions

This study is the first to investigate the symptom of recurrent episodes of leg pain of unknown aetiology (PUA) in children and adolescents with 22q11 deletion. This symptom in children with 22q11 deletion was previously dismissed as 'growing pain'. The previously unrecorded association between PUA, sleep disturbance and exercise intolerance is demonstrated in children with 22q11 deletion. The findings of this work suggest a multifactorial aetiology for all of these symptoms. More importantly, these findings suggest that mechanical therapy of associated biomechanical foot abnormalities will improve the symptoms in a significant proportion of patients. Again, this is the first work that suggests a previously unexplored therapeutic intervention for the treatment of these disruptive symptoms in children and adolescents with 22q11 deletion.

The prevalences of PUA, sleep disturbance and exercise intolerance in children and adolescents with 22q11 deletion are estimated to be 56%, 64% and 69% respectively. These are found to be significantly higher than the prevalences estimated in children and adolescents of the general population which are 37%, 13% and 6% respectively. This is the first work to measure these prevalences in the 22q11 deleted population and certainly the first to compare such prevalences with a general population sample.

The peak age for PUA in patients with 22q11 deletion was found to have a monophasic distribution, peaking at the age of 8-9 years compared with a biphasic distribution in the general population, peaking at the ages of 8-9 years and 12-13 years. The peak age for sleep disturbance in patients with 22q11 deletion was found to have a monophasic distribution, peaking at the age of 6-7 years compared with a biphasic distribution in the general population, peaking at the ages of 8-9 years and 12-13 years. The peak age for exercise intolerance in patients with 22q11 deletion was found to have a monophasic distribution, peaking at the age of 8-9 years compared with a monophasic distribution in the general population, peaking at the age 12-13 years. Although previous studies explored ages of onset and peak for growing pain in the general population, this

study is the first to suggest peak ages for PUA, sleep disturbance and exercise intolerance in children and adolescents with 22q11 deletion comparing these with general population data.

No differences in prevalence were found between females and males for PUA, sleep disturbance or exercise intolerance in children with 22q11 deletion or children of the general population.

Episodes of PUA in patients with 22q11 deletion are more likely to be of short duration lasting for less than one hour at a time, occurring daily and affecting the calf muscle area. On the other hand, episodes of PUA in children and adolescents of the general population are more likely to be of longer duration lasting 1-2 hours at a time, occur less frequently at weekly or monthly intervals and affect the knee joint area.

Episodes of PUA are likely to be of moderate severity and occur during the day or during the night in patients with 22q11 deletion and in children and adolescents of the general population. A significant proportion of patients with 22q11 deletion may not be able to rate their episodes of leg pain in terms of severity.

Episodes of sleep disturbance are more likely to occur daily in patients with 22q11 deletion in contrast with a weekly, monthly or occasional recurrence in children and adolescents of the general population.

The above findings have not been previously reported in the literature. They suggest a difference in the type or the magnitude of the underlying aetiology of PUA, sleep disturbance and exercise intolerance between patients with 22q11 deletion and children and adolescents of the general population.

Exploration of the evidence presented by this work does not support the idea that children with 22q11 deletion are more likely than children of the general population to experience unreported episodes of leg pain. This possibility however cannot be ruled out in at least a proportion of both populations.

The ages of 8-9 years and 12-13 years appear to be associated with a significant change in children with 22q11 deletion and in children of the general population. Whether this change is biological or otherwise is beyond the scope of this work.

A high percentage of patients with 22q11 deletion who experience PUA, sleep disturbance or exercise intolerance exhibited one or more biomechanical lower limb abnormalities. The lack of epidemiological data concerning biomechanical lower limb abnormalities in the general population prevented comparison between the two populations.

Although mechanical therapy of biomechanical foot abnormalities in symptomatic patients with 22q11 deletion improved the symptoms in the majority of patients, it does not appear that a single biomechanical lower limb abnormality is solely responsible for the pathogenesis of the patients' symptoms. Furthermore, it appears highly unlikely that biomechanical lower limb abnormalities are the sole aetiological factor involved and such abnormalities may even be only an aggravating factor. This work also questions the mechanism of action of mechanical therapy in alleviating symptoms in patients with 22q11 deletion, since a small number of the patients who positively responded to treatment did not exhibit biomechanical foot abnormalities.

6.2. Recommendations

It is recommended that patients with 22q11 deletion who experience recurrent leg pain of unknown aetiology, sleep disturbance or exercise intolerance should be biomechanically evaluated and a trial of mechanical therapy should be instituted. The prescribed orthotic device should be a simple insole that provides shock absorption in addition to the corrective device deemed appropriate by the clinician.

It is important to institute epidemiological studies to provide data concerning the prevalence of the various biomechanical lower limb abnormalities that may affect subjects within the general population. This should incorporate a clinical survey of symptomatic subjects with investigation of the effect of mechanical therapy on the subjects' symptoms. The model for a combined statistical and clinical study provided by this work may be used as such or modified to suit particular aims and objectives or to overcome potential shortcomings and limitations.

Studies of the possible mechanism of therapeutic action of mechanical therapy are needed, particularly since no empirical evidence of such mechanisms has been explored in the past and it has always been assumed that such therapy acts by correction or deflection.

The need for studies that address the question of pain perception differences between children with 22q11 deletion and children of the general population is highlighted by this work. In particular, quantitative sensory testing techniques could be used to investigate perception differences over a range of sensory modalities

Particular attention is drawn to the ages of 8-9 years and 12-13 years as being potentially associated with marked changes manifested as clear alteration in the prevalence of PUA, sleep disturbance and exercise intolerance and perhaps others. Research into physical, behavioural and cognitive changes during these periods may shed more light on some unexplained or poorly explained

phenomena in children with 22q11 deletion and children of the general population.

Studies of a possible relationship between blood oxygen saturation and episodes of PUA, sleep disturbance and exercise intolerance are recommended since spontaneous oxygen desaturation is one of the recognised features of 22q11 deletion and such desaturation may contribute to muscular pain and function.

Studies of the vascular and microvascular structure and function of the skeletal muscles in patients with 22q11 deletion may provide an insight into possible aetiologies of various features associated with 22q11 deletion.

This study has highlighted the problems of definition and nomenclature with the term 'growing pains'. It is recommended that a more appropriate term (such as pain of unknown aetiology) be agreed and adopted.

Finally, it is important to resolve the question of the various names given to this group of conditions, all of which have 22q11 deletion as a common aetiological factor. The various names used by various clinicians and researchers do not appear to be based on solid diagnostic criteria. It creates a great deal of confusion within families and clinicians alike. Such confusion was seen to distress many families and is therefore highly undesirable, especially considering that knowledge of this condition is not widespread within the medical community.

Appendices

Appendix I

Letters Accompanying Questionnaire

Letter to Families of patients with 22q11 deletion

Dear parent,

Leg pain in 22q11 deletions was found to be a common distressing problem to many families. The need to resolve this mystery and to propose a successful solution to it needs your cooperation. This is no different than many other issues that concern parents and professionals alike.

In my last survey, out of 150 questionnaires, 54 replies (36%) were received. 29 of those replies reported leg pain. This have left us with a certain difficulty as the 29 reports of leg pain represent 54% of the surveyed population but only 19% of the respondents. We were unable to draw a firm conclusion, as we had no idea what is happening with those who did not answer.

The questionnaire, all be it looks long, is in fact very easy to fill. It will take you no more than 10 minuets to complete. Even though we are looking at the number of children with leg pain, let me assure you that it is just as important to us to know if your child have non or some of the features we ask about.

I am indeed very grateful for your support and I hope my efforts will prove useful for many of you on the short and long term.

With kind regards

Ahmad Al-Khattat
Nene Centre for Research
University College Northampton

Letter to general population subjects

Dear Sir/Madam,

Recurrent leg pain appears to be a common complaint in childhood and teenage. It is often termed growing pains. These pains may sometimes be severe enough to interfere with usual everyday activity. Their incidence, cause and treatment remain obscure and controversial.

By completing this questionnaire, you will help us to answer one of the many unanswered questions about recurrent leg pain in young age. You will help us find out how common or uncommon is leg pain in the various age groups and what shape does this pain takes. It is also very important to us to know how many children do not suffer from leg pain. We therefore, urge you to complete the questionnaire even if your child have no problems with leg pain. This knowledge is an essential first step towards finding out the cause and the treatment of such a condition.

The questionnaire, even though appears long, is in fact very easy to complete. It should not take more than 10 minutes of your time. All information given in this questionnaire is strictly confidential and will only be viewed by the investigators.

This study has been approved by the local Medical Ethics Committee.

We would like to thank you very much for taking the time to fill in this important questionnaire.

With kind regards

Ahmad Al-Khattat
Nene Centre for Research
University College Northampton

Appendix II

The Questionnaire

Leg pain questionnaire
Information sheet

Dear Sir/Madam,

Thank you very much for taking the time to fill in this questionnaire. Before you do so, please read this information sheet.

This questionnaire is designed to give us information about the number of 22q11 patients who are suffering from leg pains. It will also allow us to compare this with the number of people who are suffering from similar leg pains in the general population.

1. **This form is to contain information about one person only. Should others like to take part in the survey, please fill in a photocopy. We would be most grateful.**

2. **If you are filling this form on behalf of your child, please encircle the phrase "your child" at the beginning of each question. If the answers contained in the questionnaire are about yourself, please encircle the word "you" at the beginning of each question.**

3. **When you have completed the form, please send it back in the provided self addressed stamped envelope or post it to the person named at the end of the questionnaire.**

4. **If you have already filled in a similar questionnaire, please fill in this revised one. This will provide further insight into the condition we are researching.**

5. **It is of vital importance for more to be learned about leg pains and lower limb abnormalities in 22q11 patients. We are therefore very interested to see and examine as many volunteers as we possibly can. We need to see patients with 22q11 deletions with and without leg pain.**

If you or your child would like to be assessed, please give your name, address and telephone number in the space provided at the end of the questionnaire. We will than get in touch with you to arrange a convenient time and place for examination.

6. **All information given in this questionnaire will be treated with strict confidentiality.**

Leg pain questionnaire

Today's date is: Day ☐☐ Month ☐☐ Year ☐☐

Date of Birth: Day ☐☐ Month ☐☐ Year ☐☐ **Gender:** Female ☐ Male ☐

Please tick the box under the most appropriate answer (s).
Please put a circle around "you" or "your child" as appropriate.

1. Are you/your child diagnosed with a 22q11 syndrome? Yes ☐ No ☐ **Genetic confirm** Yes ☐ No ☐

If yes, which one
VCFS ☐ DGS ☐ Don't know ☐ Other ☐ Please specify ----------

2. Do you / your child complain of leg pains? Yes ☐ No ☐

If no, go to question 4, otherwise, please answer the following:

Which leg ? Right ☐ left ☐ Both ☐

Where in the leg ? Knee ☐ Foot ☐ Ankle ☐ Above knee ☐ Below knee ☐

Front ☐ Back ☐

Please put a number in a box for how many times -- on average? Every day ☐ Every week ☐ Every month ☐ Others (specify below) ----------

When does the pain mostly occur? Day ☐ Night ☐ Variable ☐

On average, how long does the pain last ?

Less than hour ☐ 1-2 hours ☐ 3-6 hours ☐ 7-12 hours ☐ More than 12 hours ☐

How bad is the pain?

Mild ☐ Moderate ☐ Severe ☐ Don't know ☐

What do you think may make it worse ?

Exercise ☐ Cold weather ☐ Bad chest ☐ Don't know ☐ Others ----

---

What do you think may improve it ?

Rest ☐ Massage ☐ Pain killers ☐ Don't know ☐ Others ----

---

3. Is the cause of leg pain known ?

Yes ☐ No ☐

If yes, please state the cause.

--

4. Do you / your child wake up during the night more than expected?

Yes ☐ No ☐

If no, go to question 5, otherwise, please answer the following

Please put a number in a box for how many times on average?

Every day ☐ Every week ☐ Every month ☐ Others (specify below) ----------

Wake up complaining of leg pain?

Yes ☐ No ☐

Wake up for no obvious reason?

Yes ☐ No ☐

Wake up for other reasons?	Yes ☐	No ☐	**if yes, state the reason** ----------
Wake up kicking the leg (s)?	Yes ☐	No ☐	
Wake up rubbing the leg (s)?	Yes ☐	No ☐	
Wake up crying ?	Yes ☐	No ☐	

5. Are you / your child able to walk as much as others of similar age?

Yes ☐ No ☐

If no, please answer the following questions:

Do you/your child show any of the following during walking?

Complain of leg pain?	Yes ☐	No ☐
Lag behind?	Yes ☐	No ☐
Demand to be picked up?	Yes ☐	No ☐
Cry?	Yes ☐	No ☐

After filling this questionnaire, please send it to: Ahmad Al-Khattat, Nene Centre for Research, University College Northampton, Boughton Green Road, Northampton, NN2 7AH, England.

You only need to give your name, address and telephone number if you wish to be seen by us and we will contact you as soon as we can. We need to see 22q11 patients with and without leg pains. The interview takes about 30 minutes and sometimes we are able to visit your area. We very much appreciate your cooperation in this important investigation.

All the information given in this questionnaire will be treated with strict confidentiality.

Child's name: **Date of birth:**

Parent's name:

Address: **Telephone number:**

Appendix III

Piloting the Questionnaire

Covering letter accompanying pilot questionnaire

Dear

I would very much appreciate it if you could fill in this questionnaire and send it back to me in the provided self addressed stamped envelope. When you have filled the questionnaire, please fill in the attached scoring sheet including your thoughts about the various aspect of the questionnaire.

This questionnaire is being sent to 10 families as a pilot study. Your thoughts about the questionnaire will allow us to implement further improvements if required and have a better understanding of leg pain in VCFS/22q11 children.

I would like to thank you for your help and I hope to see you again in the near future.

Kind regards
Ahmad Al-Khattat

Scoring the leg pain questionnaire

Please give a score between 1-5 for each of the following aspects of the leg pain questionnaire. Please place the score in the corresponding box and write any comments you may have in the provided space under each question.

Ease of reading

How easy is it to read the questionnaire?

☐ 1 = Most difficult 5 = Most easy

Comprehensibility

How understandable are the questions?

☐ 1 = Not understandable 5 = Most understandable

Format

How appropriate is the lay out of the questions and the method of answer?

☐ 1 = Most inappropriate 5 = Most appropriate

Content

As a parent of a 22q11 child, how efficient is the questionnaire in covering all the aspects of your child's leg pain and related symptoms? In other words, are there any other questions we should ask?

☐ 1 = Totally inefficient 5 = Totally efficient

Length

How comfortable is the length of the leg pain questionnaire?

☐ 1 = Most uncomfortable 5 = Most comfortable

Appendix IV

Informed consent

Leg pain in 22q11 deletions research project
Family information sheet and consent form

Dear Sir/Madam,

You are thinking of taking part in this study. Please read this information sheet carefully and after you have done so, we shall be very pleased to answer any questions you may have.

Purpose and description of the study

It has been suggested that recurrent episodes of leg pain are not uncommon in patients with 22q11 deletions. It has also been suggested that the pain may improve with podiatric treatment / insole therapy.

The purpose of this research project is to investigate these claims by investigating the various aspects of leg pain in patients with 22q11 deletion including prevalence, causes, and effect of treatment. This will include 22q11 patients with and without leg pain and comparisons with non-22q11 subjects.

Taking part in this study will involve filling in an application form to become registered as a patient at the Northampton School of Podiatry. An interview will be arranged at the School of Podiatry Clinic, Northampton. During this interview, the following will take place:

1. **Complete history will be taken by asking you a number of questions.**
2. **The joints of the leg and foot will be examined during weight bearing and non-weight bearing.**
3. **The levels of any pain will be assessed**
4. **The appropriate advice and treatment will be provided. This may include exercise, insoles or other therapies.**
5. **Follow up will take place at agreed intervals (usually 2-4 weeks) to monitor the effect of the treatment and to modify it if required. During this interval, you will be asked to complete an observations diary that we will provide.**
6. **You may need to attend the clinic more than once, depending on the response to treatment. Sometimes clinics are held in different areas and we might be able to see you in or near your home. The interview may preclude you from taking part in the study, but this will not prevent you from receiving appropriate advice and treatment at Northampton School of Podiatry.**

Side effects

Sometimes, insoles may not be tolerated or may cause new aches and pains. Under such circumstances, we advice the removal of the insoles. We than review the situation and may modify or change the insoles. This usually improves the symptoms.

Benefits

In this study, you will be helping us to find out if leg pain is really a common feature of 22q11 deletions. You will also be helping us in determining the different biomechanical deformities associated with 22q11 deletions and the effect of podiatric treatment on leg pain in 22q11 deleted patients.

Consent

Participation in this study is entirely voluntary. A decision not to enter the study will not, in any way, affect your treatment from your doctor or within the Northampton School of Podiatry.

If you start in the study and than change your mind, or want to withdraw, you can do so at any time without giving a reason. This study has been examined and accepted by the local health authority's independent medical ethics committee.

All information about you will remain confidential and will only be viewed by the investigators. Should you like information to be given to other organisations, like your doctor or school, we will gladly convey such information as requested by yourself.

When you have read this leaflet please sign overleaf if you agree to take part in the study.

If you have any problems during the study you should contact

Ahmad Al-Khattat, Nene Centre for research,
Daytime telephone: (01604) 735500.
Outside working hours: (01604) 714424 telephone, fax and 24h answering machine

Nene Centre for research
Nene University College
Northampton
Boughton Green Road
Northampton, NN2 7AH
UK
(01604) 735500

Leg pain in 22q11 deletions Research Project
Consent Form

I have read and understood the information concerning this research project.

I understand that:

1. **The assessments and treatments will be provided free of charge.**
2. **Any information given or elicited will be treated as confidential information.**
3. **By signing this consent form, I agree to such information being used in the course of this research project and in any subsequent publications or presentations without divulging the identity of the patient or the family.**

Patient name **Patient signature**

Date

For children under the age of 16 years old at the time of signing this form

Parent/Guardian Name **Relation**

Signature **Date**

I confirm that I have explained to the patient the nature and effect of this investigation.

Investigator Name

Investigator Signature

Date

Appendix V

The assessment protocol

Leg pain history

Name:
Address:

Parents:
Telephone:

E-Mail:

Today's date is: Day ☐ Month ☐ Year ☐

Date of Birth: Day ☐ Month ☐ Year ☐ **Gender:** Female ☐ Male ☐

GP
Name:
Address:

Paediatrician:
Name:
Address:

Others to contact:

Please tick the box under the most appropriate answer (s).

1. Are you/your child diagnosed with a 22q11 syndrome? **Genetic confirm**

Yes ☐ No ☐ Yes ☐ No ☐

If yes, which one

VCFS ☐ DGS ☐ Don't know ☐ Other ☐ Please specify ----------

2. Do you / your child complain of leg pains?

Yes ☐ No ☐

If no, go to question 4, otherwise, please answer the following:

Which leg ? Right ☐ left ☐ Both ☐

Where in the leg ?

Knee ☐ Foot ☐ Ankle ☐ Above knee ☐ Below knee ☐ Front ☐ Back ☐

Please put a number in abox for how many times?

Every day ☐ Every week ☐ Every month ☐ Others (specify below) ----------

When does the pain mostly occur?

Day ☐ Night ☐ Variable ☐

On average, how long does the pain last ?

< 1 hour ☐ 1-2 hours ☐ 3-6 hours ☐ 7-12 hours ☐ More than 12 hours ☐ D.know ☐

How bad is the pain? Mild ☐ Moderate ☐ Severe ☐ D. know ☐

What do you think may make it worse ? Exercise ☐ Cold weather ☐ Bad chest ☐ Don't know ☐ Others ----------

What do you think may improve it ? Rest ☐ Massage ☐ Pain killers ☐ Don't know ☐ Others

3. Is the cause of leg pain known ?

Yes ☐ No ☐

If yes, please state the cause

---

4. Do you / your child wake up during the night more than expected?

Yes ☐ No ☐

If no, go to question 5, otherwise, please answer the following

Please put a number in a box for how many times?

Every day ☐ Every week ☐ Every month ☐ Others(specify below) ----------

Wake up complaining of leg pain ?

Yes ☐ No ☐

Wake up for no obvious reason? Yes ☐ No ☐

Wake up for other reasons? Yes ☐ No ☐ If yes, state the reason ----------

Wake up kicking the leg (s)? Yes ☐ No ☐

Wake up rubbing the leg (s)? Yes ☐ No ☐

Wake up crying? Yes ☐ No ☐

5. Are you / your child able to walk as much as others of similar age ?

Yes ☐ No ☐

If no, please answer the following questions:

Do you/your child show any of the following during walking?

Complain of leg pain? Yes ☐ No ☐

Lag behind? Yes ☐ No ☐

Demand to be picked up? Yes ☐ No ☐

Cry? Yes ☐ No ☐

Other features

Operations

Medications and other therapies

Leg pain examination

Toe deformities:

	First	Second	Third	Fourth	Fifth
Right					
Left					

First ray Plantarflexed ☐ Dorsiflexed ☐ Neutral ☐

FF/RF Varus ☐ Valgus ☐ Neutral ☐

Ankle dorsiflexion

	Right Ankle	Left Ankle
Knee Extended		
Knee Flexed		

Ankle equinus Soft tissue ☐ Bony ☐ Non ☐

Hip rotation

	Right hip	Left hip
External rotation		
Internal rotation		

STJ varus Yes ☐ No ☐

RF varus Yes ☐ No ☐

Tibial position Varum ☐ Valgum ☐ Neutral ☐

Tibialis posterior Anterior ☐ Not ☐

Execcive pronation in RCS med bulge ☐ flat arch ☐ many toes ☐ deep c-curve ☐

Foot print

Gait

Other features

Check list

Application

Consent

History

Examination

Footprint

Photographs

Diaries

VCFS features list

Template

Equipment check list

Consent forms.
Application forms.
Diaries.
List of VCFS features.
History and examination forms.
Tractograph.
Foot print equipment.
Cardboard.
Camera and films.
Marker pen.
White A4 paper.
Scissors.

Appendix VI

Effect of treatment feedback form

Effect of Insole Feedback Form

Name: **Date of Birth:**

Please tick the appropriate answer

1. Did you receive the insoles Yes ☐ No ☐

2. Did your child use the insoles☐☐ Yes ☐ No ☐

If no, please state the reason, if any: .....

.....

.....

If yes, please answer the following questions:

3. How long were the insoles used for? ☐

Please place the number of weeks in the opposite box

If the insoles are still in use, please tick the opposite box ☐

4. During the period of their use, please report the effect of the insoles by ticking the appropriate box

a Comfort

Very uncomfortable	Comfortable	Very comfortable
☐	☐	☐

b Effect on leg pain (If applicable)

Markedly Worse	Worse	Not improved	Slightly better	Markedly better
☐	☐	☐	☐	☐

c Effect on physical exercise

Markedly Worse	Worse	Not improved	Slightly better	Markedly better
☐	☐	☐	☐	☐

d Effect on night sleep (If applicable)	Markedly Worse	Worse	Not Improved	Slightly better	Markedly better
	☐	☐	☐	☐	☐

Thank you for completing this form. Please post it to:
Ahmad Al-Khattat, Nene Centre for Research, University College Northampton, Boughton Green Road, Northampton, NN2 7AH, UK.

Appendix VII

Letter accompanying insoles

Letter accompanying insoles

«FirstName» «LastName»
«Address1»
«Address2»
«address3»
«City»
«PostalCode»

Dear «FirstName»,

Please find insoles for «childname».

The lower grey coloured side of the insole is marked "Right" and "Left". The insoles should be placed in the shoe with the coloured covering facing upwards and the grey surface facing downwards.

Please make sure that you have registered your observations, if applicable, in at least 4 different occasions before you start using the insoles. This will enable us to measure the effect of the treatment on «childname».

Please keep taking observations until I get in touch with you again and do not hesitate to contact me if you have any queries.

Yours sincerely

Ahmad Al-Khattat

Appendix VIII

Leg pain observation diaries

Leg pains and 22q11 Research Project
Observations Diary Information Sheet

The aim of the observations diary is to monitor two particular areas related to leg pains before and after treatment. This will allow us to determine how much benefit was gained by our treatment and whether this benefit is satisfactory or not. The two areas we are interested in are the exercise tolerance and the episodes of waking up in the night.

1. Exercise tolerance:

Observing this will tell us how long is the subject able to walk before one of the leg pain indicators can be observed. Leg pain indicators that should be looked for include:

1. **A complaint of leg pains.**
2. **Lagging behind due to tiredness or laziness, but not because something has attracted their attention, for example looking into a shop window.**
3. **Demanding to be picked up or be wheeled around in a pushchair.**
4. **Demanding a rest.**
5. **Crying.**

You need to do the following:

1. **Take the subject for a usual walk, for example, shopping in the supermarket.**

2. **Look in your watch and register the time in the beginning of the walk.**

3. **Once one of the leg pain indicators is observed, look in your watch and register the time and the particular leg pain indicator observed.**

4. **If you do not have the observations diary with you, register your observations on a piece of paper and transfer them to the diary when you get home.**

5. **This should be done at least 4 times before treatment and 4 times after treatment. More than this would be very useful.**

6. **There should be no more than one observation session in any one day.**

Waking up during the night:

This may help us to determine if these waking episodes are caused by leg pains and whether or not the treatment has improved this symptom.

If you become aware that the subject woke up in the night you need to do the following:

1. **Register the day, date and time in the observations diary.**

2. **Register the reason for waking up, if known, for example, a visit to the toilet, thirst, bad dream...etc.**

3. **Watch out for and register any leg pain indicators in the observations diary. These may Include:**
    a. **A complaint of leg pain.**
    b. **Kicking the legs.**
    c. **Rubbing the legs.**
    d. **Facial expression of pain**
    e. **Crying.**

The information given in this diary are subject to similar terms as stated on your family information sheet regarding confidentiality and the right to withdraw without affecting your treatment by your doctor or the Northampton School of Podiatry.

If you have any queries or require any further information please contact:

Ahmad Al-Khattat
Nene Centre for Research
University College Northampton
Boughton Green Road
Northampton, NN2 7AH
Day time telephone: (01604) 735500
After working hours: Telephone, fax, 24h answering machine (01604) 714424.

Leg pains and 22q11 Research Project
Observations Diary for Exercise Tolerance

Day	Date	Time start walking	Observation(s) type	Time observed

Leg pains and 22q11 Research Project
Observations Diary for Waking up in the night

Day	Date	Time	Reason	Observation(s)

Appendix IX

Ethical Committee

Letter of study approval

Northamptonshire Health
Authority

Our Ref: JB/MS/98/06

Tel: Chairman (01604) 235488
Secretary (01604) 615363

13 March 1998

Dr Ahmad Al-Khattat
PhD Research Student
Nene College of Higher Education
Park Campus
Boughton Green Road
NORTHAMPTON
NN2 7AH

Dear Dr Al-Khattat

98/06 LOWER EXTRIMITY FEATURES IN PATIENTS WITH VELOCARDIOFACIAL SYNDROME/22q11 DELETIONS

Thank you for attending the Ethics Committee meeting yesterday to present your study. I am pleased to confirm that Formal Ethical Approval has been granted by the Committee for this study to proceed.

To complete our records regarding your project, would you please complete and return the form accompanying this letter.

Please also let me know if the study has to be terminated or any ethical considerations arise which need to be discussed further by the Committee.

Yours sincerely

pp. A. Houghton

A L Houghton
Deputy Chairman, Northampton Medical Research/
Ethics Committee

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