Pain, Physical and Social Functioning, and Quality of Life in Individuals with Multiple Hereditary Exostoses in the Netherlands

A National Cohort Study

A.L. Goud, MD, J. de Lange, MSc, V.A.B. Scholtes, PhD, S.K. Bulstra, MD, PhD, and S.J. Ham, MD, PhD

Investigation performed at the Department of Orthopedic Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, and the Department of Orthopedic Surgery, University Hospital, Groningen, The Netherlands

Background: This study aimed to assess pain and quality of life in a large cohort of patients with multiple hereditary exostoses.

Methods: All 322 known patients with multiple hereditary exostoses in the Netherlands were asked to participate. An age-specific questionnaire was sent to children (less than eighteen years old) and adults. The questionnaire focused on pain, daily activities, and school and/or professional situation. Adults also filled out the RAND-36 questionnaire. Results were statistically analyzed with use of the SPSS 15.0 software and with the chi-square test and multiple logistic regression. A p value of <0.05 was regarded as significant.

Results: Two hundred and eighty-three patients (88%), including 184 adults (65%) and ninety-nine children (35%), completed the questionnaire. Multiple hereditary exostoses resulted in various physical and social consequences. The majority of adults (119) were employed; however, thirty-three (28%) had changed jobs because of the symptoms of multiple hereditary exostoses and twenty-five (21%) required adjustments in their working environment. Of the sixty-five adults who were not employed, thirteen were medically unfit to work. Of eighty-five children attending school, forty-five (53%) experienced problems at school. The symptoms of multiple hereditary exostoses caused twenty-seven children (27%) and eighty-five adults (46%) to stop participating in sporting activities. Pain was the greatest problem, with sixty-two children (63%) and 152 adults (83%) who reported recent pain. On multivariate analysis, pain in adults was correlated most significantly with age and problems at work, and pain in children was correlated with the perception of the disease and problems at school. Adult patients with multiple hereditary exostoses had a lower quality of life than the Dutch reference groups, with lower scores on six of eight RAND-36 subscales.

Conclusions: Our study confirms that multiple hereditary exostoses is a chronic disease causing a profound impact on quality of life. The results suggest that pain is not the only problem associated with multiple hereditary exostoses, as it has an extensive influence on daily activities, as well as on social and psychological well-being, causing significant disability.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

A commentary by Alexandre Arkader, MD, is linked to the online version of this article at jbjs.org.

Multiple hereditary exostoses is a rare autosomal dominant disorder characterized by the presence of multiple osteochondromas. These usually occur at the metaphysis of long bones, but all bone formed without membranes may be involved. Pain is the most frequent indication for surgery and may be caused by bursitis, tendinitis, and compression of nerves or vessels[1-4]. Osteochondromas can also cause limb-length discrepancies, skeletal deformities, limited joint motion, and axial deviation[2,3]. In adults, there is a risk of malignant transformation of osteochondroma to chondrosarcoma, with an estimated prevalence of 1% to 5%[1,2].

Most published studies on multiple hereditary exostoses have described the efficacy of specific surgical techniques or the specification of deformities. Little is known with regard to the general health status of these patients or the severity of pain and loss of function and how multiple hereditary exostoses influences the activities of daily life. Only one study has suggested that the debilitation and reduction in quality of life are severe[5].

We hypothesized that the consequences in patients with multiple hereditary exostoses were more substantial than generally presumed. A nationwide cohort study was undertaken in the Netherlands among all patients with multiple hereditary exostoses to gain more insight into the unknown consequences of this disease.

Materials and Methods

The Human Research Committee of Groningen University Medical Center approved the study protocol. All 322 known patients with multiple hereditary exostoses were asked to participate. These patients were either members of the Dutch MHE (Multiple Hereditary Exostoses) patient coalition or were treated in one of three national referral centers for this disease (Onze Lieve Vrouwe Gasthuis, Amsterdam; Maxima Medical Centre, Veldhoven; or University Medical Center, Groningen, The Netherlands). After providing written informed consent, all positive respondents received a standardized questionnaire.

Two different questionnaires were used: one specifically addressed children and one addressed adults. Children were defined as individuals younger than eighteen years of age. An initial set of questionnaires was sent to a pilot group (five children and five adults) to assess whether the questionnaire appealed to the so-called SMART (Specific, Measurable, Acceptable, Realistic, and Time-consuming) principles[6]. The responses were incorporated into the final questionnaire.

Both questionnaires included questions about demographic characteristics, family history, and medical history related to multiple hereditary exostoses, including the number of surgical procedures and the occurrence of malignant degeneration. The questionnaires further queried with regard to physical (activities of daily life and sports participation), social (family situation and occupation for adults and school for children), and financial (medical insurance for adults) consequences. There were multiple questions on pain perception, which were based on previous research by Darilek et al.[5]. The adult questionnaire further contained the RAND 36-Item Health Survey (RAND-36). The RAND-36 is a generic, self-reported measure of quality of life, including the same items as the Medical Outcomes Study Short Form-36, and although the scoring procedures are somewhat different, the effects on final scores are minimal[7]. The RAND-36 consists of thirty-six items and generates eight subscales: physical functioning, social functioning, role limitations due to physical functioning, role limitations due to emotional problems, mental health, vitality, pain, and general health perceptions[8]. The two role-limitation subscales measure problems with work or other daily activities, as a result of either physical or emotional problems. One last item—health change—assesses the perceived change over the last year in health status. The RAND-36 scores are converted to a percentage ranging from 0 to 100, with higher values indicating higher levels of functioning or well-being. The RAND-36 is a reliable and valid instrument, widely used in the evaluation of patients with somatic diseases. The present study used the eight subscales and compared the results with random representative samples of 1063 adults from a municipality (Emmen) in the northern part of the Netherlands[9] (the mean age was 44.1 years; range, eighteen to eighty-nine years; and 65% were female), 4172 adults from Amsterdam[10] (the mean age was 43.1 years, and 54% were female), and a random, nationwide sample of 1742 adults (the mean age was 47.6, and 56% were male). As the item *health change* was not included in the last two studies[9,10], it was excluded from the comparison.

The mean time to complete the forms was twenty minutes (range, five to sixty minutes) for children and twenty-nine minutes (range, ten to 120 minutes) for adults.

Statistical Methods

All results were entered in a database, and statistical analysis was performed with use SPSS software (version 15.0; SPSS, Chicago, Illinois). Descriptive statistics (frequencies and means) were used to present results on demographics, family history, medical history related to multiple hereditary exostoses, physical and social consequences, pain, and quality of life in adults and children. Various factors of these parameters were analyzed with regard to their potential relationship with the existence of physical and social consequences and pain. Potential relationships were analyzed with use of the chi-square test. Variables showing a significant relationship were additionally analyzed in a multiple logistic regression analysis, to evaluate which of them best predicted the occurrence of pain. Separate analyses were performed for the adult and pediatric populations. Quality-of-life scores (measured with the RAND-36) were compared with the reference scores with use of the unpaired Student t test. Overall significance was set at a p value of <0.05.

Source of Funding

There was no external funding.

Results

Two hundred and eighty-three patients (88%) returned the completed questionnaire. One hundred and sixty-six patients (59%) were members of the patient coalition and 117 (41%) were contacted through one of the referral hospitals. One hundred and eighty-four (65%) of the participants were adults and ninety-nine (35%) were children; 155 (55%) were female. Baseline demographics, family history, and medical history related to multiple hereditary exostoses are listed in Table I. Seventy-two percent recorded a positive family history for multiple hereditary exostoses. The mean height (169.5 cm) and weight (72.0 kg) in the adult group were significantly less than that in the general Dutch population (173.9 cm and 75.6 kg)[11]. Osteochondromas had been removed in 88% of adults and 48% of children at the time of evaluation. Malignant transformation was recorded in thirteen adult patients (7%).

Sixty-seven (61%) of 109 adult women had given birth to one or more children. Thirty-four (51%) experienced problems during labor because of multiple hereditary exostoses, necessitating a cesarean section in twenty-three (34%), which is substantially higher than that in the general Dutch population (13.5%)[12].

Physical and Social Consequences

Sports Participation

Fifty-seven children (58%) participated in sports at the time of evaluation. Twenty-seven children (27%) had stopped their sporting activities because of problems related to multiple

hereditary exostoses; the most frequent activities to be discontinued were gymnastics (eight children) and soccer (four). Problems with sports activities were significantly related to age, with older children having more problems than younger children ($p < 0.04$).

Eighty-five adults (46%) performed sporting activities. Another eighty-five had stopped their participation in sporting activities because of problems related to multiple hereditary exostoses; the activites most frequently discontinued were team sports such as soccer (thirteen adults), volleyball (five), and handball (five).

Occupation

One hundred and nineteen adults (65%) had paid employment at the time of evaluation (see Appendix). In twenty-five adults (21%), adjustments to the workplace, including special chairs, computer equipment, and special tasks, had been necessary. Thirty-three individuals (28%) had changed jobs because of symptoms of multiple hereditary exostoses. Sixty-seven individuals (56%) had had problems at one time or another during their occupation, including a workload that was too heavy (twenty-nine; 24%), pain (ten; 8%), and functional impairment (eight; 7%). Of the sixty-five adults who were not employed, thirteen were medically unfit to work.

School

Of the eighty-five children attending school, forty-five (53%) reported having problems at school. Most frequently mentioned were problems with physical education (twenty-four children), writing (twelve), and working with computers (twelve). Seven children (8%) reported being bullied because of their disorder. Eleven children received special help, such as laptops or specific school programs.

Insurance

Thirty-two adults (17%) encountered problems with medical insurance or had to pay higher premiums because of multiple hereditary exostoses. Eight were not accepted at all, whereas four received only medical insurance that excluded multiple hereditary exostoses. The problems with medical insurance were significantly related to age, with older patients having more problems than younger patients ($p < 0.045$).

Discomfort and Pain

In the group of children, only fifteen (15%) experienced no problems with their disorder. Thirty-three children (33%) perceived their disorder as moderately or very annoying (see Appendix).

Eighty-three percent of adults (152) and 63% of children (sixty-two) had experienced pain in the thirty days before filling out the questionnaire. Details with regard to pain are listed in the Appendix.

Pain in Adults

Among 152 adults with recent pain, the most common location was the lower extremities (49%), followed by shoulder girdle (14%), upper extremity (9%), pelvic region (9%), and ribs or back (8%). The activity that aggravated pain most was walking (49%), followed by lifting objects (29%), climbing stairs (17%), physical endurance (13%), cycling (13%), sitting (13%), and housekeeping (9%). Sixty-six percent of adults tried to reduce pain by resting, and 34% used heat application. Forty-six adults (30%) reported taking pain medication on a regular basis.

The interference of pain with activities of daily life, sleep, social contacts, and mood for the 152 adults is listed in the Appendix.

Pain was inversely related to age. Pain was positively related to problems at work and to the presence of deformities (see Appendix). Multiple logistic regression analysis showed that the experience of pain was best predicted by problems at work ($p < 0.0001$) and age ($p = 0.0024$) (Table II). Problems at work showed an odds ratio of 0.615. In other words, adjusted for age level, the odds of adult patients having pain are approximately 1.626 times (1/0.615) higher in patients with problems at work than in those without such problems. Age level showed an odds ratio of 0.094; thus, with adjustment for the influence of problems at work, the odds of having pain is approximately 10.6 times (1/0.094) higher in younger patients than in older patients (per ten years). This final model explained 14.37% (R^2) of the variance in the chance of pain from multiple hereditary exostoses in the adult group.

Pain in Children

In sixty-two children with recent pain, the most common location was also the lower extremity (60%), followed by the upper extremity (15%) and axial skeleton (9%). The most frequently reported activity that aggravated pain was walking (52%), followed by sports or physical education (16%), playing (16%), cycling (13%), and lifting objects (13%). Thirteen children (21%) reported sleeping problems because of pain during the previous thirty days. Twenty-nine children (47%) tried to reduce the pain by resting, and seventeen (27%) used heat application. Eight children (13%) reported taking pain medication on a regular basis. In the pediatric group, pain was related to a more negative perception of the disease, problems at school, and a greater number of surgical procedures (see Appendix). According to the multiple logistic regression analysis, pain was best predicted by the perception of the disease ($p = 0.0039$) and problems at school ($p = 0.0284$) (Table II). Perception of the disease showed an odds ratio of 2.872 (Table II), with the odds of experiencing pain about 2.872 times higher in children with a more negative perception of the disease than in those with a more positive perception. Problems at school had an odds ratio of 0, with the odds of experiencing pain in children about 3.48 times (1/0.287) higher in children with problems at school than in children without such problems. This final model explained 25.8% (R^2) of the variance in the chance of pain from multiple hereditary exostoses in the children's group.

RAND-36

Using the RAND-36 questionnaire, we found a significantly lower outcome in six subclasses (physical functioning, social functioning, role limitations due to physical functioning,

TABLE I Patient Characteristics, Family History, and Data Related to Multiple Hereditary Exostoses

	Total	Adults	Children
Number	283	184	99
Sex			
Men and boys	128 (45%)	75 (41%)	53 (54%)
Women and girls	155 (55%)	109 (59%)	46 (46%)
Mean age (range) *(yr)*	29.1 (1 to 80)	39.7 (18 to 80)	9.4 (1 to 17)
Mean height (standard deviation) *(cm)*		169.5 (9.07)	
Male		176.6 (7.72)	
Female		164.6 (6.26)	
Mean body weight (standard deviation) *(kg)*		72.0 (15.90)	
Male		78.4 (12.86)	
Female		67.4 (14.74)	
Affected individuals with children		111 (60%)	
Sons with the disorder		58 (50%) of 117	
Daughters with the disorder		73 (58%) of 126	
Family history			
Having a parent with the disorder	203 (72%)	131 (71%)	72 (73%)
No parent with the disorder	62 (22%)	40 (22%)	22 (22%)
Unknown	18 (6%)	13 (7%)	5 (5%)
Brothers and/or sisters with the disorder		210 (48%) of 442	53 (54%) of 99
Comorbidity *(no. of patients)*		46 (25%)	16 (16%)
Pulmonary problems		8 (4%)	2 (2%)
Spondylarthritis		6 (3%)	
Allergy		6 (3%)	2 (2%)
Hypertension		5 (3%)	
Breast cancer		3 (3%) of 109	
Location of osteochondromas			
Upper extremity		165 (90%)	92 (93%)
Shoulder girdle		119 (65%)	64 (65%)
Pelvic girdle		89 (48%)	28 (28%)
Lower extremity		181 (98%)	90 (91%)
Rib and/or spine		81 (44%)	59 (60%)
Removal of osteochondromas		161 (88%)	48 (48%)
Adults			
Procedure at <18 yr		128 (70%)	
≥3 operations		67 (36%)	
Procedure at ≥18 yr		124 (67%)	
≥3 operations		48 (26%)	
Children			
First procedure at <6 yr			12 (25%)
First procedure at 6-11 yr			26 (54%)
First procedure at 12-18 yr			10 (21%)
≥3 operations			14 (14%)
Location			
Upper extremity		149 (81%)	33 (69%)
Lower extremity		88 (48%)	33 (69%)
Ribs and/or vertebrae		21 (11%)	4 (8%)
Pelvic girdle		20 (11%)	4 (8%)
Shoulder girdle		48 (26%)	3 (6%)

TABLE I (*continued*)

	Total	Adults	Children
Deformities	225 (80%)	148 (80%)	77 (78%)
Forearm	124 (44%)	81 (44%)	43 (43%)
Knee region	113 (40%)	80 (43%)	33 (33%)
Angle region	91 (32%)	61 (33%)	30 (30%)
Fingers	50 (18%)	28 (15%)	22 (22%)
Correction of deformity	63 (22%)	45 (24%)	18 (18%)
Chondrosarcoma		13 (7%)	
Mean age at time of diagnosis (range) *(yr)*		35 (20-50)	
Female		8 (61.5%)	
Male		5 (38.5%)	
Location			
Pelvic region		6 (46%)	
Feet		2 (15%)	
Knee region		2 (15%)	
Femur		2 (15%)	
Humerus		1 (8%)	
Education			
Less than high school		12 (7%)	
High school graduate		99 (54%)	
Some college		71 (39%)	
Unknown		2 (1%)	
Specific equipment or adjustments at home		62 (34%)	18 (18%)
Semi-orthopaedic shoes		25 (14%)	3 (3%)
Inlays		13 (7%)	9 (9%)
Cane or crutches		22 (12%)	1 (1%)
Wheelchair		8 (4%)	
Wrist brace		5 (3%)	3 (3%)
Adjustments to home		9 (5%)	
Other		23 (13%)	6 (6%)

vitality, pain, and general health perception) for the group with multiple hereditary exostoses compared with all three reference groups. The greatest differences were for physical functioning and pain. Only for the subclasses of role limitations due to emotional problems and mental health as well as for health change were no significant differences found (Table III).

Discussion

This comprehensive study of patients with multiple hereditary exostoses in the Netherlands confirms that the disorder is not only associated with pain but also has a profound negative influence on physical and social functioning and quality of life. Multiple hereditary exostoses significantly impacts a wide range of aspects, both personally and professionally.

In the literature, the prevalence of multiple hereditary exostoses is estimated to be approximately one in 50,000[1,13]. The expected number of cases in the Netherlands, with a population of seventeen million, would be around 340. The fact that we identified 322 patients may imply that the prevalence is higher in the Netherlands. However, as the patient coalition is highly active and modern communication methods are readily used by this relatively young population, we believe a considerable number of afflicted individuals in our country have been contacted for this survey. As 88% completed and returned the questionnaires, this study appears highly representative of the Dutch population with multiple hereditary exostoses.

Only one previous study, to our knowledge, has specifically addressed quality-of-life issues in multiple hereditary exostoses[5]. In that series of 293 patients with multiple hereditary exostoses, 84% reported having pain, slightly higher than the 76% we found. Thirty-one percent of the adults with pain in our series reported having had pain every day during the last month, which was also less than the 45.3% in the previous series. Individuals in the series described by Darilek et al.[5] seemed more afflicted in the comparison of pain ratings and the interference of pain with general activity, sleep, social interactions, and mood. However, the response rate in their series was only 39% compared with 88% in the present study. This may have led to selection bias as disease severity may influence the willingness to participate in a questionnaire-based survey. Nevertheless, the results from both studies are impressive, and our data corroborate the findings of the previous study.

TABLE II Final Multiple Logistic Regression Models for Presence of Pain in Adults and Children

	Beta	Standard Error	Wald	Degrees of Freedom	Significance (P Value)	Exponent Beta (or Odds Ratio)	95% Confidence Interval for Exponent Beta	
							Lower	Higher
Adult model								
Problems at work	−2.367	1.524	21.765	1	<0.0001	0.615	0.449	0.842
Age level	−0.487	0.161	9.187	1	0.0024	0.094	0.021	0.411
Intercept	7.111	1.524	9.8622	1	0.0017			
Child model								
Perception of MHE*	1.055	0.3655	8.3359	1	0.0039	2.872	1.403	5.879
Problems at school	−1.247	0.5690	4.8012	1	0.0284	0.287	0.094	0.0877
Intercept	0.262	1.3310	0.0389	1	0.8437			

*MHE = multiple hereditary exostoses.

TABLE III Scores on the RAND-36

Dimensions	MHE Group*	Emmen		National		Amsterdam	
		Score*	T Score†	Score*	T Score†	Score*	T Score†
Physical functioning	64.2 ± 25.6	81.9 ± 23.2	−9.23‡	83.0 ± 22.8	−10.3‡	85.2 ± 23.1	−11.8‡
Social functioning	80.4 ± 23.3	86.9 ± 20.5	−3.83‡	84.0 ± 22.4	−2.03‡	85.1 ± 21.5	−2.84‡
Role limitations-physical	67.7 ± 39.2	79.4 ± 35.5	−3.95‡	76.4 ± 36.3	−2.98‡	79.5 ± 35.4	−4.27‡
Role limitations-emotional	82.4 ± 34.8	84.1 ± 32.3	−0.63	82.3 ± 32.9	0.04	83.1 ± 32.7	−0.27
Mental health	76.2 ± 14.5	76.8 ± 18.4	−0.41	76.8 ± 17.4	−0.44	75.9 ± 17.0	0.22
Vitality	61.3 ± 17.6	67.4 ± 19.9	−3.82‡	68.6 ± 19.3	−4.81‡	68.6 ± 19.2	−4.94‡
Pain	63.7 ± 24.0	79.5 ± 25.6	−7.67‡	76.4 ± 36.3	−4.57‡	80.5 ± 24.4	−3.32‡
General health perception	66.5 ± 21.5	72.7 ± 22.7	−3.35‡	70.7 ± 20.7	−2.56‡	71.3 ± 20.8	−2.99‡
Health change	50.1 ± 20.8	52.4 ± 19.4	−1.44	NA		NA	

*The scores, which have a possible range of 0 to 100, are given as the mean and the standard deviation. MHE = multiple hereditary exostoses. NA = not available. †The T score represents the comparison of the scores of MHE patients and those of the population of Emmen, the general population (national), and the population of Amsterdam. Negative numbers denote worse scoring of the MHE patients, and positive numbers denote better scoring of MHE patients compared with group specified. ‡Denotes significance.

Interestingly, more adults than children experienced pain (83% compared with 63%). Together with the finding that two-thirds of adults reported having had surgery after the age of eighteen years, these observations establish that problems associated with multiple hereditary exostoses persist into adulthood and continue after the growth of osteochondromas has ceased.

As pain was highly prevalent in both groups, we tried to identify predictors of pain by means of multiple regression analysis. The severity of pain in adults was significantly associated with problems at work and the presence of deformities. The problems at work were reported as having a grave impact on the quality of life. In the adult group, in contrast to the findings of Darilek et al.[5], no relationship was found between pain and previous surgery or with the number of surgical procedures. In the pediatric population, we found a significant association between pain and problems at school and disease perception. The predictive power of the models was weak in both patient groups, explaining only 14% to 26% of the total variance. This means that the chance of pain from multiple hereditary exostoses is not strongly influenced by the identified predictors (age and work problems among adults and disease perception and school problems among children).

Besides the effect of pain, multiple hereditary exostoses has a severe impact on daily life. Half of those with paid employment had experienced problems, with 28% who had to stop their activities or change jobs and 21% who needed adjustments to the workplace. The choice of occupation seemed to be guided by problems associated with multiple hereditary

exostoses, as most individuals did not perform heavy manual labor. Office duties or clerical work, occupations in the field of education, and management and information and communication technology were reported most often. This career choice is of interest, as frequently occurring deformities and functional limitations of the forearm may lead to problems during repetitive manual activities.

Patients with multiple hereditary exostoses were substantially incapacitated in their ability to perform sports. This is relevant since the capability of younger patients to participate in sports decreased significantly because of pain or functional limitations as they grew older. In adults, 50% of individuals who were previously active in sports had quit because of problems related to the multiple hereditary exostoses. Participation in sports that required frequent running or turning and team sports, rather than individual sports, was stopped. Whether the discontinuation of the team sports was the result of the physical activity itself or whether other problems played a role in the decision is unclear.

Of the children in school, more than half encountered serious problems, especially with physical education, writing, and computer-related tasks. Although it seems obvious that these activities may be hindered by functional impairment and pain, the number was higher than expected. Furthermore, only a limited number of children received specific equipment or adapted school programs to diminish these problems. This, and the fact that a considerable number of children were bullied because of their disorder, reflects, in our opinion, the lack of acknowledgment in the school setting with regard to the problems associated with multiple hereditary exostoses.

Self-reported validated health surveys play an increasingly important role in evaluating patient functioning, quality of life, and health status. Using the RAND-36, we found a significant negative outcome in six subclasses for the group with multiple hereditary exostoses compared with three control groups. The greatest differences were found for physical functioning and pain. No significant differences in the subscales for role limitations due to emotional and mental health were found in any of the comparisons. In addition to confirming that pain was the dominant problem in multiple hereditary exostoses, our findings also confirmed that social and physical functioning scores were lower for patients with the disease than for those in the control groups, reflecting the problems at work and during sports that are experienced by individuals with multiple hereditary exostoses. These factors may also be influenced by the presence of deformities and/or the number of prior surgical procedures. Vitality scores were also lower for patients with multiple hereditary exostoses than for those in the control groups, which may also give rise to problems at work or during sports.

This study shows that multiple hereditary exostoses is a chronic disease that hampers social functioning. As cognitive and behavioral problem-solving interventions have been shown to benefit patients with chronic pain syndromes, this type of intervention could potentially benefit patients with multiple hereditary exostoses[14]. More studies with longer follow-up are needed to gain insight into the need for professional support in managing physical and psychosocial problems of patients with multiple hereditary exostoses.

Several demographic characteristics and conditions related to multiple hereditary exostoses were of interest. There was a slight predominance of females (55%) in our representative survey, in contrast to older studies indicating a higher prevalence of males[3,15,16]. More recent studies found no evidence of sex predominance[1,2,6,17]. Wicklund et al. suggested that the initial observation could reflect ascertainment bias, attributable to more severe clinical manifestation of multiple hereditary exostoses in males[2]. Milder disease in females could be the result of earlier completion of puberty and growth arrest[1]. We found no significant differences between males and females with respect to pain, surgery, multiple hereditary exostoses-related complications, or in the results from the RAND-36.

We specifically asked participants about comorbidities, which could be an important finding in the pathophysiology of the disorder or the life expectancy. In the adult group, pulmonary problems were reported most frequently. This could be due to chronic obstructive pulmonary disease but might also result from osteochondroma formation on the ribs. The only malignant disease reported without relation to osteochondroma was breast cancer, which was noted by three female patients. As one in eight women in the Netherlands will develop breast cancer during her lifetime, the rate of three of 109 female patients in our series of relatively young patients was not higher than expected.

Patients with multiple hereditary exostoses are often of short stature, with most studies describing heights that were 0.5 to 1.0 standard deviation below the mean[2,3,18]. In concordance with the literature, the average height (and standard deviation) of the adults in our series was 4.4 ± 0.48 cm less than that of the general population[2]. The mean body weight was also substantially less, which is attributable to the shorter stature.

According to the literature, approximately 75% of patients with the disease have a clinically recognizable osseous deformity, most commonly involving the forearm (50%), ankle (45%), or knee (20%)[1]. In our series, respective numbers were in the same range: 80% had a visible deformity, involving the forearm (44%), ankle (32%), or knee (40%).

In two reported series of patients with multiple hereditary exostoses, 66% to 74% had undergone at least one surgical procedure and the average was two or three procedures[1,2]. In the present series, 88% of adult patients and 48% of children had had one or more surgical procedures, averaging 3.5 and 2.3 procedures per individual, respectively.

More than half of the female participants who had one or more children reported complications during pregnancy and/or delivery. Cesarean section was necessary in 34% of these women, which was 2.5 times higher than that in the general Dutch population[11]. Wicklund et al. reported similar results[2]. In their series, two-thirds of women with multiple hereditary exostoses reported delivery by cesarean section, with 29% of these procedures being secondary to pelvic osteochondromas. According to the authors, women with multiple hereditary exostoses were at least twice as likely as the general population to have a cesarean section.

Malignant transformation of osteochondroma into chondrosarcoma has been estimated to occur in 1% to 6% of patients with multiple hereditary exostoses, with the pelvis being the site most often involved[1,2,19]. In our series, secondary chondrosarcoma was reported by thirteen (7%) of 184 adults. However, as a considerable number of adults in our group were relatively young, the lifetime incidence may be higher. The percentage found in our study should, however, be regarded with some caution, as patients who are more severely afflicted, as in those with malignant transformation, might be more inclined to participate in a quality-of-life survey. The mean age at the time of diagnosis of malignant degeneration is younger than that for chondrosarcoma in general[20]. The mean age at the time of chondrosarcoma diagnosis in the present series was thirty-five years, in concordance with Ochsner[21], who found that the mean age at the time of diagnosis of malignant degeneration was thirty-one years for fifty-nine patients with multiple hereditary exostoses.

The main limitation of the present study is its subjective character. As quality of life is by definition a subjective matter, and the sample obtained is highly representative of patients with multiple hereditary exostoses in the Netherlands, this does not appear to affect the results. Whether these results in the Dutch setting can be extrapolated worldwide is uncertain because of possible cultural, occupational, and geographic differences. A further limitation of the study is that, unlike the adult questionnaire, which included the RAND-36, no validated pediatric quality-of-life assessment tool was used. The general applicability of the results of our study may be further hampered by the fact that, even with questions in the questionnaire referring to any perceived temporal change in the patient's situation, the results provide information mainly at a single time point. Further research into the changes in quality-of-life issues over time is currently being performed. This longitudinal survey may also reveal correlations among phenotypic expression (i.e., disease severity), clinical findings, and quality of life, thereby enabling us to devise a more objective tool to predict outcome.

In conclusion, this study confirms that multiple hereditary exostoses is a chronic, often painful disease that has a more profound impact on quality of life than is generally suspected. Our results suggest that pain is not the only important problem associated with multiple hereditary exostoses, but pain has an extensive influence on the activities of daily life as well as on social and psychological well-being, causing significant disability.

Appendix

eA Tables showing employment status of adults; children's perception of their experience with the disorder; the prevalence, frequency, and severity of pain associated with the disease; pain interference ratings in adults; and significant relationships between pain and other variables are available with the online version of this article as a data supplement at jbjs.org. ■

A.L. Goud, MD
V.A.B. Scholtes, PhD
S.J. Ham, MD, PhD
Department of Orthopedic Surgery,
Onze Lieve Vrouwe Gasthuis, P.O. Box 95500,
1090 HM Amsterdam, The Netherlands.
E-mail address for A.L. Goud: annemariegoud@hotmail.com

J. de Lange, MSc
MHE-MO Patient Coalition, P. O. Box 95500,
1090 HM, Amsterdam, The Netherlands

S.K. Bulstra, MD, PhD
Department of Orthopedic Surgery, University Hospital,
Groningen, P.O. Box 30.001, 9700 RB,
Groningen, The Netherlands

References

1. Schmale GA, Conrad EU 3rd, Raskind WH. The natural history of hereditary multiple exostoses. J Bone Joint Surg Am. 1994;76:986-92.
2. Wicklund CL, Pauli RM, Johnston D, Hecht JT. Natural history study of hereditary multiple exostoses. Am J Med Genet. 1995;55:43-6.
3. Shapiro F, Simon S, Glimcher MJ. Hereditary multiple exostoses. Anthropometric, roentgenographic, and clinical aspects. J Bone Joint Surg Am. 1979;61:815-24.
4. Stieber JR, Dormans JP. Manifestations of hereditary multiple exostoses. J Am Acad Orthop Surg. 2005;13:110-20.
5. Darilek S, Wicklund C, Novy D, Scott A, Gambello M, Johnston D, Hecht J. Hereditary multiple exostosis and pain. J Pediatr Orthop. 2005;25:369-76.
6. Doran GT. There's a S.M.A.R.T. way to write management's goals and objectives. Management Rev. 1981;70:35-6.
7. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51:903-12.
8. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ. 1993;2:217-27.
9. Van der Zee K, Sanderman R. RAND-36. Groningen: Northern Centre for Health Care Research, University of Groningen, the Netherlands. 1993:1-28.
10. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51:1055-68.
11. Vademecum Gezondheidsstatistiek Nederland. Dutch Central Bureau of Statistics (CBS). Voorburg; 1998.
12. Dutch Society of Obstetrics and Gynaecology (NVOG). The quality of obstetric care and the number of caesarian sections in your hospital. 2005.
13. Hennekam RC. Hereditary multiple exostoses. J Med Genet. 1991;28:262-6.
14. McCracken LM, Turk DC. Behavioral and cognitive-behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. Spine (Phila Pa 1976). 2002;27:2564-73.
15. Jaffe HL. Hereditary multiple exostosis. Arch Pathol. 1943;36:335-57.
16. Solomon L. Hereditary multiple exostosis. Am J Hum Genet. 1964;16:351-63.
17. Peterson HA. Multiple hereditary osteochondromata. Clin Orthop Relat Res. 1989;239:222-30.
18. Solomon L. Bone growth in diaphysial aclasis. J Bone Joint Surg Br. 1961;43:700-16.
19. Voutsinas S, Wynne-Davies R. The infrequency of malignant disease in diaphyseal aclasis and neurofibromatosis. J Med Genet. 1983;20:345-9.
20. Björnsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. Cancer. 1998;83:2105-19.
21. Ochsner PE. [Multiple cartilaginous exostoses and neoplastic degeneration: review of the literature (author's transl)]. Z Orthop Ihre Grenzgeb. 1978;116:369-78. German.