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The impact of hereditary multiple exostoses on quality of life, satisfaction, global health status, and pain

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Abstract
Purpose The aim of the study was to evaluate quality of life (QOL), global health status, pain, and level of satisfaction in patients with hereditary multiple exostoses (HME), and to correlate the association between the severity of diseases and age, sex, number of surgical procedures, and number of exostoses.
Methods The data of 50 patients with HME were retrospectively evaluated and recorded. QOL was evaluated with the Short-Form Health Survey (SF-12) questionnaire, the 12-Item General Health Questionnaire (GHQ-12), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF); intensity of pain was measured using the visual analogue scale (VAS). The association of age, gender, pain, quality of life, number of exostoses, and number of surgical procedures were evaluated and correlated.
Results Mean number of exostoses in our patient's cohort resulted 18.12 ± 8.60, and every patient underwent to a mean of 5.62 ± 5.74 surgical procedures for the exostoses. Mean VAS resulted 5.16 ± 2.90. Considering SF-12, mental (MCS) and physical (PCS) component resulted, respectively, 45.36 ± 10.76 and 38.73 ± 11.09, while GHQ-12 and Q-LES-Q-SF were 15.48 ± 4.70 and 45.28 ± 9.55, respectively. We found a significant positive correlation between the number of exostoses and the number of surgical procedures ($p < 0.001$), a significant positive correlation between the number of surgical procedures and GHQ-12 ($p = 0.422$) and VAS ($p = 0.0011$), and a negative correlation between the number of surgical procedures and PCS ($p = 0.0257$) and between age and GHQ-12 ($p = 0.0385$).
Conclusions We can conclude that HME impact on patient quality of life as measured by the MCS and PCS scores similar to the disability associated with osteoarthritis in the mental component and tumors or diabetes as regards the physical component. Moreover, we found no difference in patients' quality of life as regards number of exostoses, age, and surgical procedure, but we found that women have a worse response as regards the psychological side than men.

Keywords Hereditary multiple exostoses · Quality of life · Global health status · Rare disease · Pain · Satisfaction · Surgical procedure

Introduction

Hereditary multiple exostoses (HME) is a rare disorder, thought to arise in around 1 in 50,000 individuals, and males and females are affected in equal numbers [1]. HME is inherited as an autosomal dominant genetic condition and the abnormal gene can be inherited from either parent or can be the result of a new mutation in the affected individual. Approximately, 10% of cases of HME are thought to be the result of new mutations. At present two genes, EXT1 and EXT2, are known to show mutations in

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HME patients and it is thought that these genes function as tumor suppressors [2]. Exostoses are covered with cartilage and appear in the growth zones of the long bones, and these growths may vary in size and number. [3]. The symptoms are very frequently related to the size of the exostoses: in fact, with the presence of small exostoses, the patient may be totally asymptomatic. However, in more severe cases, the growths may cause deformities of the forearm, knees, ankles, spine, and pelvis, imposing upon nerves, tendons, and blood vessels, and interfering with movement or circulation, causing substantial pain as a result of pinched nerves or compressed tendons. Surgical correction is often required, particularly for bowing of the forearm and ankle, and approximately, 40% of affected individuals have mild short stature [4].

The bony growths stop after puberty and the risk of malignant tumors is approximately 1–5% [5]. Most published studies on multiple hereditary exostoses focus on results on the efficacy of surgical techniques or the specification of deformities [6–9], while a few studies report on the general health status of these patients and how the severity of pain and loss of function affect quality of life and the activities of daily life of these patients [10, 11].

The aim of the study was to evaluate quality of life (QOL), global health status, and level of satisfaction in patients with hereditary multiple exostoses, and to assess their relationship with independent epidemiologic parameters.

Methods

A retrospective chart review of clinical and radiographic records was performed. HME were diagnosed on the basis of clinical and radiographic evaluation. The inclusion criteria for this retrospective epidemiologic case series were: patients older than 16 years; diagnosis of 2 or more exostoses; and ability to give informed consent. Exclusion criteria were: additional surgical procedures in addition to the removal of the exostoses, such as hip replacement, limb lengthening or arthrodesis, haemophilia, rheumatoid arthritis, severe metabolic disorders, ongoing chemotherapy, radiation treatment or immunosuppression, and pregnancy or lactation. All patients completed the following evaluations: Visual Analogue Pain Score (VAS), Short-Form Health Survey (SF-12), 12-Item General Health Questionnaire (GHQ-12), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) [12–15]. SF-12 is a generic questionnaire on quality of life that is not disease, age, or treatment specific. It evaluates the subjective perception of the individual in relation to the concepts of health and wellness. To simplify, the assessment is divided into a Physical Component Summary (PCS) and Mental Component summary (MCS) [13]. Moreover, we compared the results obtained from our cohort, the SF-12, with a sample of the Italian population to assess the differences found [16]. GHQ-12 was used to assess the inability to perform the normal health function. Attention is focused on the change in the normal psychic functioning of the subject and assessing personality disorders or patterns of adaptation associated with distress [12]. The Q-LES-Q-SF is among the most frequently used outcome measures in psychiatry research. It is a generic, self-reported QOL measure assessing the physical health, subjective feelings, leisure activities, social relationships, general activities, satisfaction with medications, and life satisfaction domains [15].

Moreover, sex, age, number of exostoses, and number of surgical procedures caused by exostoses for each patient were recorded. We considered only surgical procedures of excision and removal of the exostoses due to pain, impingement and compression of tendon, nerve, or blood vessels confirmed by anatomopathological examination. However, the location and the size of the exostoses were not assessed. The association with, age, gender, pain, quality of life, and number of surgical procedures was then evaluated.

This study received institutional review board approval.

The statistical analysis was performed by MATLAB statistical toolbox, version 2008 (MathWorks, Natick, MA, USA) for Windows at 32 bit, on a sample of 50 patients; 62% females and 38% males, with ages into range 17–81, with mean around 40 y.o. and standard deviation (SD) around 13 y.o. The statistical tests were performed with Student's T test for paired and unpaired data and χ^2 with Yates correction for comparison of two proportions of unpaired data. Furthermore, we evaluated significant correlation with Pearson's linear correlation coefficient R, where the correspondent p values were computed with the T Student test, under null hypothesis of Pearson's linear correlation coefficient $R = 0$ between independent (age, sex, number of exostoses, and number of surgical procedure) and dependent parameters (VAS, SF-12, GHQ-12, and Q-LES-Q-SF).

We considered significant all statistical tests with p value <0.05.

Results

Of 61 patients screened for eligibility, 50 satisfied the inclusion criteria and were enrolled in the study; 62% of the patients were females and 38% males, with mean age 40 years (SD $\pm$ 13; range 17–81). Of the 11 excluded patients, 4 underwent total hip replacement, 2 underwent total knee replacement, 2 were younger than 16 years, 2 women were pregnant, and 1 was hemophilic.

Table 1 Clinical parameters score for patient groups described by mean ± SD (standard deviation)

Group	Nr. exostoses	Nr. operations	VAS	MCS	PCS	GHQ-12	Q-LES-Q-SF
Total	18.12 ± 8.60	5.62 ± 5.74	5.16 ± 2.90	45.36 ± 10.76	38.73 ± 11.09	15.48 ± 4.70	45.28 ± 9.55

Mean number of exostoses in our patient group resulted 18.12 ± 8.60, and every patient underwent to a mean of 5.62 ± 5.74 surgical procedures for the exostoses. Mean VAS resulted 5.16 ± 2.90. Considering SF-12, MCS and PCS resulted, respectively, 45.36 ± 10.76 and 38.73 ± 11.09, while GHQ-12 and Q-LES-Q-SF were 15.48±4.70 and 45.28 ± 9.55, respectively.

Results are summarized in Table 1.

In our group of patients, we found a significant positive correlation between the number of exostoses and the number of surgical procedures ($R = 0.497$, $p < 0.001$), a significant correlation between the number of surgical procedures and GHQ-12 ($R = 0.289$, $p = 0.422$) and VAS ($R = 0.448$, $p = 0.0011$), and a negative correlation between the number of surgical procedures and PCS ($R = -0.315$, $p = 0.0257$) and between age and GHQ-12 ($R = -0.294$, $p = 0.0385$).

Results are summarized in Table 2.

Table 2 Significant linear correlation among clinical parameters into our patient's cohort

Correlations	Total group	
	R	*p* value
Exostoses/Nr. operations	0.497	<0.001
Nr. operations/GHQ 12	0.289	0.0422
Nr. operations/PCS	−0.315	0.0257
Nr. operations/VAS	0.448	0.0011
Age/GHQ-12	−0.294	0.0385

Table 3 *T* Student test for unpaired data, for comparison parameters between ES− and ES+

Parameters	ES− ($n = 24$)	ES+ ($n = 26$)	*p* value
Nr. operations	2.54	7.54	**0.0061***
VAS	4.04	6.19	**0.0041***
MCS	47.56	43.33	0.0859
PCS	41.19	36.46	0.0686
GHQ-12	15.71	15.27	0.3737
Q-LES-Q-SF	44.33	46.15	0.2553

Bold represent significant test values

ES− group of patients with fewer than 20 exostoses, *ES*+ group of patients with 20 or more exostoses

* p value < 0.05

Number of exostoses

We found a significant positive association between the number of operations and the number of exostoses ($R = 0.497$, $p < 0.001$).

We considered 24 patients with a mean age of 39 years (62.50% females and 37.50% male, SD ± 10; range 21–57), represented by all patients with fewer than 20 exostoses (ES−) and 26 patients with a mean age of 41 years (61.54% females and 38.46% male, SD ± 16; range 17–81) represented by all patients with a higher number of exostoses (ES+) or equal to 20, and verified the differences of all parameters. The cut-off value to define the two groups was set to 20, as 20 was the median value of our data set. In ES+ group, the number of surgical procedures and VAS were significantly greater ($p < 0.05$) than those of the ES− group. Results are summarized in Table 3.

No significant correlations were found in the ES− group, while in ES+ group, the number of surgical procedures was positively related with VAS ($R = 0.0490$, $p = 0.011$) and GHQ-12 ($R = 0.405$, $p = 0.0404$).

Number of surgical procedures

We considered the INT− group consisted of 21 patients, mean age of 45 years (range 20–81; SD ± 14; 51.14% females and 49.86% males), represented by all patients with fewer than 4 interventions and INT+ group, consisted of 29 patients with a mean age of 36 years (range 17–57; SD ± 11; 65.52% females and 34.47% males) represented by all patients with a greater number of interventions or equal to 4, and verified the differences of all parameters. The cut-off value to define the two groups was set to 4, as 4 was the median value of our data set. In the INT+ group, patients presented a number of exostoses significantly greater than those of the INT− group ($p < 0.05$). Results are summarized in Table 4. No significant correlations were found in either groups ($p > 0.05$).

Age

No significant correlations were found between age and all the others parameters ($p > 0.05$).

Then, the initial sample of 50 patients was divided into two groups, defining the group of patients under 40 (UF), (i.e., those with less than or equal to 40 years), consisting

Table 4 *T* Student test for unpaired data, for comparison parameters between INT+ and INT

Parameters	Int− ($n = 21$)	Int + ($n = 29$)	p value
Nr. exostoses	14.14	21.00	**0.0023***
VAS	4.52	5.62	0.097
MCS	46.70	44.39	0.231
PCS	40.44	37.50	0.183
GHQ-12	14.86	15.93	0.218
Q-LES-Q-SF	45.24	45.31	0.490

Bold represent significant test values

INT− group of patients with fewer than 4 interventions, *INT*+ group, of patients with a greater number of interventions or equal to 4

* p value < 0.05

Table 5 *T* Student test for unpaired data, for comparison parameters between OF and UF

Parameters	UF ($n = 27$)	OF ($n = 23$)	p value
Exostoses	17.89	18.39	0.421
Nr. operations	6.07	5.09	0.277
VAS	4.93	5.43	0.273
MCS	44.64	46.21	0.308
PCS	38.93	28.50	0.446
GHQ-12	16.30	14.52	0.095
Q-LES-Q-SF	47.07	43.17	0.078

OF group of patients with more than 40 years, *UF* group of patients withof less than 40 years

of 27 patients, 19 (70.37%) females and 8 (29.63%) males, with a mean age of 30 years (SD ± 6; range 17–39) and the group of patients over 40 (OF) consisting of 23 patients, 12 (52.17%) females and 11 (47.83%) males, with a mean age of 52 years (SD ± 8; range 41–81). The cut-off value to define the two groups was set to 40 years, equal to the average value of the age of our sample of patients. Between UF and OF groups, we found no significant differences, regarding number of exostoses, number of surgical procedures, VAS, MCS, PCS, GHQ-12, and Q-LES-Q-SF. Results are summarized in Table 5. Stratified analysis for UF and OF patient subgroup revealed a significant positive correlation between the number of exostoses and the number of surgical procedures ($p < 0.05$) in both the two subgroups, but in the UF group, we found a significant negative correlation between the number of exostoses and PCS ($R = -0.422$, $p = 0.0281$) and age and GHQ-12 ($R = -0.501$, $p = 0.0077$), while in the OF group, the number of surgical procedures is positively correlated with VAS ($R = 0.463$, $p = 0.0260$) (Table 6).

Table 7 *T* Student test for unpaired data, for comparison parameters between MG and FG

Parameters	MG ($n = 19$)	FG ($n = 31$)	p value
Exostoses	18.00	18.19	0.470
Nr. operations	5.68	5.58	0.478
VAS	4.63	5.48	0.162
MCS	49.06	43.09	**0.0292***
PCS	44.00	35.51	**0.0039***
GHQ-12	14.47	16.10	0.0952
Q-LES-Q-SF	48.63	43.23	**0.0267***

Bold represent significant test values

MG male group, *FG* female group

* p value < 0.05

Gender

Based on all our samples, we found that the percentage of the patients affected by HME was predominantly of female sex (females: 62% vs. males: 38%, p value = 0.0278, $\chi 2$ test with Yates correction). We compared the clinical outcomes of the male group (MG), composed of 19 patients with a mean age of 45 years, (range 25–81, SD ± 13) with the female group (FG), consisting of 31 patients with a mean age of 37 (range 17–57, SD ± 11). In the male group, MCS, PCS, and Q-SF-Q-LES were significantly higher than those of the female group ($p < 0.05$). Moreover, for the male group, despite being statistically equal to the female group in terms of number of exostoses ($p > 0.05$) and of interventions ($p > 0.05$), this group presented a better state, both in terms of physical and mental and quality of life (Q-LES-Q-SF) ($p < 0.05$).

Results are summarized in Table 7.

Stratified analysis for the MG and FG patient subgroup revealed in both groups a significant positive correlation

Table 6 Significant linear correlation among clinical parameters into UF and OF

UF			OF		
Correlations	R	p value	Correlations	R	p value
Exostoses/Nr. operations	0.572	0.0018	Exostoses/Nr. operations	0.460	0.0272
Exostoses/PCS	−0.422	0.0281	Nr. operations/VAS	0.463	0.0260
Age/GHQ-12	−0.501	0.0077			

OF group of patients with more than 40 years, *UF* group of patients ofwith less than 40 years

Table 8 Significant linear correlation among clinical parameters into MG and FG

MG group			FG group		
Correlations	*R*	*p* value	Correlations	*R*	*p* value
Exostoses/Nr. operations	0.550	0.0148	Exostoses/Nr. operations	0.488	0.0054
Nr. operations/VAS	0.425	0.0211	Nr. operations/VAS	0.380	0.0348
Nr. operations/PCS	0.572	0.0105	Nr. operations/MCS	−0.363	0.0450

MG male group, *FG* female group

between the number of exostoses and the number of surgical procedures ($p < 0.05$) and the number of surgical procedures and VAS ($p < 0.05$), but in the MG, the number of operations was positively correlated with PCS ($R = 0.572$, $p = 0.0105$), while in the FG with MCS ($R = -0.363$, $p = 0.045$). In Table 8, the significant correlations between the two groups are summarized.

Discussion

Treating HME is a therapeutic challenge for the orthopaedic surgeon, who, in most cases, has to handle patients dissatisfied in their daily lives hoping to see improvements following the surgery.

The aim of our study was to report quality of life of patients with HME and to assess their relationship with epidemiologic independent factors, such as age, sex, number of exostoses, and number of procedure.

In literature, only a few studies have evaluated the quality of life in patients with HME [10, 11], and to our best knowledge, no study has investigated the relationship between surgical interventions and quality of life. In 2012, Gould [10] evaluated the quality of life in a Dutch national cohort of patients with HME and an age-specific questionnaire was sent to 322 patients, both children and adults. The questionnaire was completed by 283 patients (88%), of which 184 were adults (65%) and 99 children (35%). Most of the adults were employed (119), and 33 (28%) had changed jobs due to the symptoms of the disease, while 25 (21%) required adjustments in their working place. As regards unemployed adults, 13 were unfit to work. Of 85 children attending school, 45 (53%) reported problems at school. Sports activities were impossible due to symptoms of multiple hereditary exostoses for 27 children (27%) and 85 adults (46%). In adults, pain resulted correlated with age and problems at work, while in children, it was correlated with problems at school. Considering RAND-36 subscales, adult patients had lower scores resulting in a lower quality of life than the Dutch reference groups The author concluded that multiple hereditary exostoses are a chronic disease causing a profound impact on quality of life and 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.

Recently Chhina [11] explored the QOL among adults and children with HME in 57 adults and 43 children. The adult HME population had lower scores than both the US and Canadian general population in all domains except for emotional role limitations. Short-Form-6D utility scores indicate the quality of life for some individuals as near death, and for others, it is comparable or better than individuals with rheumatoid arthritis. Children with HME scored less than the US general population; particularly, lower scores were seen in bodily pain and emotional self-esteem.

In our patient cohort, with a mean age of 40 years, we found that average VAS resulted 5.16, while MCS and PCS were, respectively, 45.36 and 38.73. GHQ-12 and Q-LES-Q-SF were found to be 15.48 and 45.28, respectively. Moreover, we found a correlation between number of exostoses and number of surgical procedures, with patients with a higher number of exososteses, being more often subjected to surgery, but it is interesting to observe that increase in surgery decreases the quality of life (PCS, MCS, GHQ-12). In addition, aging leads to a worsening of psychological conditions (GHQ-12) in patients with HME. As regards age, the disease affects patients in the same way in all parameters evaluated, but it is interesting to note that in UF patients, the number of exostoses is related with the physical component of daily living.

Comparing men and women instead, it emerges that women are more affected with regard to the psychological aspect than men (MCS, Q-LES-Q-SF), in fact, women show a significant negative correlation between the number of surgical procedure and MCS, while in MG, the number of exostoses is related with MCS. This shows how women respond psychologically differently than men. Both groups show how the number of surgical procedure has a negative effect on the pain (VAS).

In patients with a greater number of exostoses, it is seen that they have more pain and are subjected to a greater number of interventions, but the number of exostoses has no affect with regard to the quality of life and the psychological component. In the same way, also comparing

Table 9 Comparison between the values of SF-12 in patients with HME and other diseases in the Italian population [16]

Disease	MCS	PCS
No pathology	52.79	53.74
Osteoarthritis	45.78	42.26
Lombosciatalgia	45.73	43.13
Hypertension	45.61	42.69
Diabetes	45.11	40.22
Migraine	44.58	45.96
Tumors	41.64	37.87
Nervous disorders	33.76	42.29
Our sample, HME	**45.36**	**38.73**

Bold represents sample of patients

patients according to the number of interventions, we have not found strong association of factors.

Comparing our results with a national survey brought to light how severely HME impact quality of life. Specifically, in an Italian study of 10,546 persons with a mean age of 35–44 years, patients had a mean MCS of 50.83 and PCS of 52.94 [16].

In addition, comparing our SF-12 outcomes with some of the most common chronic diseases, the results are even more interesting: in fact, patients with diabetes report value of 45.11 and 40.22, respectively, for MCS and PCS, while orthopaedic pathologies mean results, respectively, for osteoarthritis and lombosciatalgia were 45.78 and 45.73 for MCS and 42.26 and 43.13 for PCS [16]. The most significant values that we found regarded the physical component; in this case, the reference value that is closest to our group is in patients affected by tumors, which show a mean value of PCS of 37.87 [16].Our results show that HME can be compared mentally to other orthopaedic disorders, such as sciatica and arthritis, which physically interfere in daily living activities in the same way as chronic diseases like cancer and diabetes.

The comparison with the reference values is shown in Table 9.

As regards the GHQ-12 questionnaire, we found a borderline value, whereas the value of 15 was the threshold to consider the presence of disturbances at the level of the general state of health [12].

This data can be backed-up by an article published in 2004 which shows that the positivity of the GHQ-12 is linked to the number of life events detected and the number of medical visits [17]. In our sample, we are faced with a number of patients with major life events, such as surgery, as well as numerous specialized medical examinations that may affect this result. This is confirmed also by the correlation we found between the number of surgical procedures and GHQ-12.

Similarly, interesting is when we come to evaluate the results obtained from the Q-LES-Q-SF. In this case, the value obtained by our sample (45.28) when compared to the studies in existing literature is similar to a sample of patients with generalized anxiety disorders. Wyrwich, in 2009, reported a mean value of Q-LES-Q-SF of 51.16 from a sample of 2588 patients with generalized anxiety disorders, similar to our sample of patients [18]. This shows how patients with HME live with a state of anxiety and decreased ability to enjoy life and to be satisfied, thus affecting normal daily activities.

We can conclude that HME impact patient' quality of life as measured by the MCS and PCS scores similar to the disability associated with osteoarthritis in the mental component and tumors or diabetes as regards the physical component; moreover, we found no difference in patients' quality of life as regards number of exostoses, age, and surgical procedure, but women have a worse response from the psychological side in respect to men.

This study has several limitations: first of all, the relatively small number of patients that allow for limited subpopulation analysis. Another important limitation is the lack of sub-analysis based on location and size of the exostoses. We tried to overcome this limitation considering only surgical procedures of removal of exostoses. Moreover, only one clinical assessment did not allow us to measure over time the change of clinical parameters. Finally, the lack of sport activity assessment, particularly in young patients, is a further limitation of our study. Future studies will focus on the evaluation of sports activity in patients with HME and the return to the sport in patients who underwent surgery for exostoses also considering the type of sports activity (high or low impact) and time taken to return to sports.

Conclusions

To date, our study is the first to assess quality of life in an Italian cohort of patients with HME, and we can conclude that HME impact patient' quality of life as measured by the MCS and PCS scores similar to the disability associated with osteoarthritis in the mental component and tumors or diabetes as regards the physical component; moreover, we found no difference in patients' quality of life as number of exostoses, age, and surgical procedure, but found that women have a worse response from the psychological side in respect to men.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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