Journal of Orthopaedics 15 (2018) 927–930

Contents lists available at ScienceDirect

Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

Effect of multiple hereditary exostoses on sports activity in children

Riccardo D'Ambrosi[a,b,*], Camilla Caldarini[c], Vincenza Ragone[d], Renato Mario Facchini[e]

[a] Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy
[b] IRCCS Istituto Ortopedico Galeazzi, Milan, Italy
[c] Azienda Socio Sanitaria Territoriale Gaetano Pini, Milan, Italy
[d] IRCCS Policlinico San Donato, San Donato Milanese, Italy
[e] Università degli Studi di Milano, Milan, Italy

ARTICLE INFO

Keywords:
Hereditary multiple exostoses
Multiple osteochondromas
Sport
Physical activity
Rare disease
Clinical case-control study

ABSTRACT

Objective: The purpose of this clinical case-control study was to assess the level of sports activity in children with hereditary multiple exostoses (HME) and to compare with the degree of physical activity in children of the same age without pathology.
Methods: A case-control study was designed. Cases were drawn from children with HME diagnosed on the basis of clinical and radiographic evaluation with an age less then 12 years. Controls were chosen from a group of children with the same age and a negative family history for HME. All patients and controls were completed with the help of parents using the following evaluations: Tegner Activity Level Scale and University of California Los Angeles (UCLA) activity scale.
Results: A total of 154 individuals participated (54 cases and 100 controls). In the case groups, the mean age was 9.07; the mean number of exostoses resulted 29.51, while the mean value of UCLA and Tegner score resulted respectively 6.04 and 5.09. In the controls, the mean age was 8.88; mean UCLA and Tegner resulted respectively 7.17 and 5.64. Comparing the two groups, the only difference was between UCLA score ($p = 0.0053$). Moreover, comparing the results between female children affected by HME and female controls, we found a significant difference as regards UCLA score ($p = 0.0045$).
Conclusion: Children affected by HME reported lower sports activity, in particular as regards female patients. Moreover, physical activity is not correlated with any other independent factor leading different patients to a similar level of ability in performing sport.
Study design: Level III – Case Control Study.

1. Introduction

Multiple hereditary exostoses (MHE) were described for the first time in 1814 by Boyer in his *Related diseases and surgical operations of their choosing*.[1] HME is a rare pathology characterized by development of multiple osteochondromas, benign bone tumors, caused by mutations in genes EXT1 and EXT2.[2,3] The exact prevalence of HME is unknown because many patients are asymptomatic and diagnosis may be difficult. In Caucasians an estimated prevalence of HME around 0.9 to 2 individuals per 100,000 has been reported, but a higher prevalence has been identified in isolated populations such as the Chamorros (Guam) and the Ojibway Indian community of Pauingassi (Manitoba, Canada).[4–6]

The osteochondromas are not present at birth, but develop in the first decade of life affecting long and flat bones and leading to dysmetry and malformation.[7]

In recent years several articles have highlighted how patients affected by HME report pain and discomfort with a low quality of life, both in children and adults, but literature is scarce regarding clinical studies about sports and physical activity in patients with HME.[8–10]

The purpose of this clinical case-control study was to assess the level of sports activity in children with HME and to compare with the degree of physical activity in children of the same age without pathology.

2. Material & methods

A clinical case-control study was designed.[11] Cases were drawn from children with HME diagnosed on the basis of clinical and radiographic evaluation with an age less than 12 years. Each diagnosis was verified by a consultant pediatric radiologist and consultant pediatric

* Corresponding author. IRCCS Istituto Ortopedico Galeazzi, Milan, Italy.
E-mail addresses: riccardo.dambrosi@hotmail.it (R. D'Ambrosi), camilla.caldarini@tiscali.it (C. Caldarini), ragone.vincenza@inwind.it (V. Ragone), Renato.facchini@unimi.it (R.M. Facchini).

https://doi.org/10.1016/j.jor.2018.08.029
Received 10 May 2018; Accepted 16 August 2018
Available online 24 August 2018

orthopaedic surgeon based on radiographic appearances and clinical features. The inclusion criteria for this clinical study were: patients younger than 12 years, clinical and radiological diagnosis of 2 or more exostoses. Exclusion criteria were: patients older than 12 years old, additional surgical procedures in addition to the removal of the exostoses, haemophilia, rheumatoid arthritis, severe metabolic disorders.

Controls were chosen from a group of children with the same age and sex and a negative family history for HME. This clinical case-control study was conducted on the basis of the STROBE statement guidelines.[12]

All patients and controls were completed with the help of one or both parents, using the following evaluations:

- Tegner Activity Level Scale[13]
- University of California, Los Angeles (UCLA) activity scale[14]

Tegner activity level scale is a graduated list of activities of daily living, recreation, and competitive sports. The patient is asked to select the level of participation that best describes their current level of activity and that before injury. The score varies from 0 to 10. A score of 0 represents sick leave or disability pension because of knee problems, whereas a score of 10 corresponds to participation in national and international elite competitive sports > 6 score can only be achieved if the person participates in recreational or competitive sport. The UCLA scale is a simple scale ranging from 1 to 10. The patient indicates her or his most appropriate activity level, with 1 defined as “no physical activity, dependent on others” and 10 defined as “regular participation in impact sports.”

Moreover, sex, age and number of exostoses, for each patient were recorded. However, the location and the size of the exostoses were not assessed. The association with gender, number of exostoses and physical activities was then evaluated and correlated. Both parents of the children signed an informed consent for participation in the study. All procedures performed in the 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.

2.1. Statistical analysis

Statistical analysis was conducted using a statistical software (SPSS version 17, SPSS Inc., Chicago, IL, USA). The statistical tests were performed with Student's T test for paired and 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. We considered significant all statistical tests with p-value < 0.05.

3. Results

A total of 154 individuals participated (54 cases and 100 controls). In case groups the mean age was 9.07, 26 (48.14%) of the patients were male and 28 (51.86%) females; the mean number of exostoses resulted 29.51, while the mean value of UCLA and Tegner score resulted respectively 6.04 and 5.09. In the controls the mean age was 8.88, 51 (51%) cases were male, while 49 (49%) were female. Mean UCLA and Tegner resulted respectively 7.17 and 5.64. Comparing the two groups the only difference that we found was between the number of exostoses (p < 0.001) and UCLA score (p = 0.0053). Results are reported in Table 1.

3.1. Gender

3.1.1. Male

Comparing the results in our cohort between male children affected by HME and male controls, we found no differences, except for the number of exostoses (p < 0.001). Results are reported in Table 2.

Table 1
Clinical parameters score for cases and controls described by mean ± SD (standard deviation). T Student test for unpaired data, for comparison parameters between cases and controls.

Variables	Cases		Controls		p-value
	Mean	Standard deviation	Mean	Standard deviation	
Gender[a]	0.52	0.504	0.49	0.499	0.738
Age	9.07	2.01	8.88	1,61	0.478
Number of Exostoses	29.51	20.65	0	0	< 0.001[b]
Tegner Score	5,09	2,89	5.64	1,77	0.202
UCLA	6.04	2.64	7.17	1.99	0.0053[b]

[a] To calculate the mean and standard deviation of the gender we have attributed an arbitrary value of 0 to the male and 1 to the female.
[b] p-value < 0.05; UCLA = University of California, Los Angeles activity scale.

Table 2
T Student test for unpaired data, for comparison parameters between Male cases and Male Controls.

Variables	Cases (Male) n = 28		Controls (Male) n = 49		p-value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age	8.88	1.50	8.92	1.61	0.92
Number of Exostoses	31.27	21.58	0	0	< 0.001[a]
Tegner Score	5.08	2.69	6.08	1.85	0.10
UCLA	6.42	2.60	7.14	2.25	0.25

UCLA = University of California, Los Angeles activity scale.
[a] p-value < 0.05.

3.1.2. Female

Comparing the results in our cohort between female children affected by HME and female controls, we found a significant difference as regards number of exostoses (p < 0.001) and UCLA score (p = 0.0045). Results are reported in Table 3.

3.1.3. Correlations

In patients affected by HME the only significant correlation that we found was between UCLA and Tegner Score (R = 0.759, p-value < 0.001). Results are reported in Table 4.

4. Discussion

The aim of this clinical case-control study was to assess the level of sports and physical activity in children with HME and comparing with a

Table 3
T Student test for unpaired data, for comparison parameters between Female Cases and Female Control.

Variables	Cases (Female) n = 26		Controls (Female) n = 51		p-value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age	9.25	1.66	8.84	1.62	0.30
Number of Exostoses	27.89	18.81	0	0	< 0.001[a]
Tegner Score	5.11	2.92	5.18	1.56	0.90
UCLA	5.68	2.36	7.20	1.56	0.0045[a]

UCLA = University of California, Los Angeles activity scale.
[a] p-value < 0.05.

Table 4
Significant linear correlation among clinical parameters in patients affected by Hereditary Multiple Exostoses.

Variables	Age	Gender	Number of exostoses	Tegner	UCLA
Age	1	0.114	- 0.153	0.085	0.199
Gender	0.114	1	−0.083	0.005	−0.149
Number of exostoses	−0.153	−0.083	1	−0.167	−0.244.
Tegner	0.085	0.005	−0.167	1	0.759[a]
UCLA	0.198	0.148	−0.244.	0.759[a]	1

UCLA = University of California, Los Angeles activity scale.
[a] p-value < 0.05.

control group of children of the same age with negative family history for HME. The main finding in our study was the difference as regards UCLA score between the cases and the controls ($p < 0.05$); considering the gender this difference was not present in male cases versus male controls ($p > 0.05$), but was significant matching female cases and controls ($p < 0.05$). No other significant difference was found among the groups, even by performing a stratified analysis of the gender. Moreover, in our cohort we found that sports in children affected by HME, is not correlated with any other independent factor leading different patients to a similar level of physical activity.

This difference in the amount of sport, in respect to the control group, can be traced in some way to the characteristics of children suffering from HME. In 2015 Staal et al. hypothesized that the diminished stature in adults with multiple osteochondromas is due to a systemic influence, leading to early skeletal maturation and early closure of the growth plate. Fifty radiographs in children with HME were collected and evaluated to calculate the skeletal age according to the Greulich–Pyle bone scale. The author noted that children aged between 3 and 12 years had a significantly lower skeletal age compared to their calendar age and that skeletal maturation in children with HME therefore differs from their peers.[15]

Previously Clement et al. showed that the height of individuals with HME compared with a normal population varies according to age, with preadolescence (2–9 y.o.) patients being taller than expected.[16]

Moreover the same author also explains how the severity of the disease between the two sexes changes, in contrast with our finding in which girls presented a lower level of physical activity; in fact in 2014 Clement et al. reported that male patients with an EXT1genotype had a significantly greater number of exostoses affecting their hands, distal radius, proximal humerus, scapular and ribs compared to female patients with the same genotype.[16]

In recent years several articles have reported surgical techniques in order to improve the functionality and quality of life in children with HME, but no article has evaluated sport in these subjects. These interventions are often performed to prevent severe deformities, arthrosis and dysmetria.[17–22]

In 2012 Goud et al. evaluated pain and quality of life in a large cohort of patients with HME. The author found that 57 children (58%) participated in sports at the time of evaluation. Twenty-seven children (27%) had stopped their sporting activities due to HME; 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.[9]

In the same year, Chhina et al. evaluated health-related quality of life both in children and adults with HME and compared with relevant Canadian and US population norms. It is interesting to note that children scored less than the control groups; in particular lower score were reported for pain and emotional component. Differently from our results, male children had lower scores that female, except for mental health.[8]

The importance of physical activity to relieve pain in patients with exostoses has been reported in a recent case report that focuses on how eccentric training might decrease pain, increase range of motion, muscle strength, and functional levels in patients with HME.[23]

The major limitation of the study is the lack of sub-analysis based on location and size of the exostoses. Future studies will have to focus on creating ad hoc assessment scales for children with hereditary multiple exostoses and in evaluating the ideal sporting activity in these subjects, in order to improve the functionality and relieve pain.

5. Conclusions

Children affected by HME reported lower sports activity, in particular as regards female patients. Moreover, physical activity is not correlated with any other independent factor leading different patients to similar level of ability in performing sport.

Conflicts of interest

The authors declare that they have no conflicts of interest. The first author has full control of all primary data and agrees to allow the journal to review their data if requested.

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.

Funding

None.

Disclosure

The manuscript is original and is not under consideration for publication by any person or entity, including electronic publisher.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jor.2018.08.029.

References

1. Boyer A. *Related Diseases and Surgical Operations of Their Choosing.* Paris: Ve Mingeret; 1814:594.
2. Pacifici M. Hereditary multiple exostoses: new insights into pathogenesis, clinical complications, and potential treatments. *Curr Osteoporos Rep.* 2017;15:142–152.
3. Beltrami G, Ristori G, Scoccianti G, et al. Hereditary Multiple Exostoses: a review of clinical appearance and metabolic pattern. *Clin Cases Miner Bone Metab.* 2016;3:110–118.
4. Stieber JR, Dormans JP. Manifestations of hereditary multiple exostoses. *J Am Acad Orthop Surg.* 2005;13:110–120.
5. Black B, Dooley J, Pyper A, Reed M. Multiple hereditary exostoses: an epidemiologic study of an isolated community in Manitoba. *Clin Orthop.* 1993;287:212–217.
6. Krooth RS, Macklin MT, Hilbish TF. Diaphyseal aclasis (multiple exostosis) on Guam. *Am J Hum Genet.* 1961;13:340–347.
7. Bovée JV. Multiple osteochondromas. *Orphanet J Rare Dis.* 2008;13(3):3.
8. Chhina H, Davis JC, Alvarez CM. Health-related quality of life in people with hereditary multiple exostoses. *J Pediatr Orthop.* 2012;32:210–214.
9. Goud AL, de Lange J, Scholtes VA, et al. Pain, physical and social functioning, and quality of life in individuals with multiple hereditary exostoses in The Netherlands: a national cohort study. *J Bone Joint Surg Am.* 2012;94:1013–1020.
10. D'Ambrosi R, Ragone V, Caldarini C, et al. The impact of hereditary multiple exostoses on quality of life, satisfaction, global health status, and pain. *Arch Orthop Trauma Surg.* 2017;137:209–215.
11. Marx RG, Wilson SM, Swiontkowski MF. Updating the assignment of levels of evidence. *J Bone Joint Surg Am.* 2015;97:1–2.
12. von Elm E, Altman DG, Egger M, et al. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;6:344–349.
13. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;198:43–49.

14. Zahiri CA, Schmalzried TP, Szuszczewicz ES, et al. Assessing activity in joint replacement patients. *J Arthroplasty.* 1998;13:890–895.
15. Staal HM, Goud AL, van der Woude HJ, et al. Skeletal maturity of children with multiple osteochondromas: is diminished stature due to a systemic influence? *J Child Orthop.* 2015;9:397–402.
16. Clement ND, Duckworth AD, Baker AD, et al. Skeletal growth patterns in hereditary multiple exostoses: a natural history. *J Pediatr Orthop B.* 2012;21:150–154.
17. Clement ND, Porter DE. Hereditary multiple exostoses: anatomical distribution and burden of exostoses is dependent upon genotype and gender. *Scot Med J.* 2014;59:35–44.
18. Kang S, Kim JY, Park SS. Outcomes of hemiepiphyseal stapling for genu valgum deformities in patients with multiple hereditary exostoses: a comparative study of patients with deformities of idiopathic cause. *J Pediatr Orthop.* 2017;37:265–271.
19. Kelly JP, James MA. Radiographic outcomes of hemiepiphyseal stapling for distal radius deformity due to multiple hereditary exostoses. *J Pediatr Orthop.* 2016;36:42–47.
20. Lee DY, Kim JI, Song MH, et al. Fibular lengthening for the management of translational talus instability in hereditarymultiple exostoses patients. *J Pediatr Orthop.* 2014;34:726–732.
21. D'Ambrosi R, Barbato A, Caldarini C, et al. Gradual ulnar lengthening in children with multiple exostoses and radial head dislocation: results at skeletal maturity. *J Child Orthop.* 2016;2016(10):127–133.
22. Guindani N, Eberhardt O, Wirth T, et al. Surgical dislocation for pediatric and adolescent hip deformity: clinical and radiographical results at 3 years follow-up. *Arch Orthop Trauma Surg.* 2017;137:471–479.
23. Kanik ZH, Gunaydin G, Sozlu U, et al. Eccentric training as an adjunct to rehabilitation program for hereditary multiple exostoses: a case report. *J Clin Diagn Res.* 2016;10:YD03–4.