

Eligibility for competitive sport medical certification of children with severe hemophilia: Italian observational study

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Abstract. *Background ad aim of work:* the position of Italian law regarding participation of prophylactically treated hemophiliacs to organized sport trainings and competitions remains unclear and this study focuses on the eligibility of pediatric patients in particular. *Methods:* 16 patients aged 3 to 15 years old, with severe haemophilia and prophylaxis starting age of $20,2 \pm 2,2$ months were enrolled. Weight, height, body mass index (BMI) and joint status (Hemophilia Joint Health Score (HJHS) and Haemophilia Early Arthropathy Detection with UltraSound, HEAD-US score) of patients were evaluated at start (T0) and after 12 months (T12) of a HIITS sport activity program. *Results:* All patients qualified for Italian competitive sport medical certification. Their weight and height increased after 12 months, without an increase in BMI (T0= 17,2; T1= 18,7; $p>0,05$). HJHS score did not change significantly (T0: 1.6 ± 1 ; T1: 2.1 ± 1.3 ; $p>0.05$). All children were right-handed and atrophy for the muscles of the right elbow significantly decreased (no atrophy seen at T0 in 4 of 16 patients and at T1 in 8 of 16 patients; $p=0.045$). *Conclusions:* Hemophilic children, prophylactically treated, are capable to be included in sport groups and physical activity programs.

Key words: Children, Sport, Hemophilia, Arthropathy.

Introduction

Hemophilia is an X-linked recessive bleeding disorder typically caused by a deficiency of coagulation factor VIII (Haemophilia A, HA) or IX (Haemophilia B, HB). The incidence of HA is estimated to be 1 in 5,000 males, and that of HB 1 in 30,000 males (1, 2). Based on coagulation factor activity, hemophilia is subdivided into severe (factor activity <0.01 IU/ml), moderate (0.01–0.05 IU/ml) and mild (>0.05 –0.35–0.40 IU/ml) forms. Patients

with severe hemophilia often develop spontaneous and recurrent bleeds into the joints (hemarthrosis), muscles and other soft tissues, while those with mild–moderate hemophilia tend to experience bleeding related to trauma and surgery (3). Prophylactic replacement of the missing factor is the optimal treatment for hemophilia in the developed world and it effectively reduces the bleeding frequency and its consequences (4, 5). The primary objective of the prophylactic regimen for the treatment of patients with haemophilia is reaching a level of circulating FVIII of

at least 1% (6). However, high performance physical activity may pose a higher risk of bleeding events or hemarthrosis in patients, in particular in pediatric patients. Prophylactic regimens should be tailored based on individual patient characteristics and addressed to reach a higher concentration of circulating FVIII, as during high-rate physical activity the risk of bleeding is increased (7). Importantly, prophylactic treatment has allowed patients with hemophilia to live nearly normal lives. Sports and physical activity were historically denied to children with severe hemophilia, given the risk of sports-associated trauma and subsequent hemorrhages and morbidity (8). Recent studies have documented the physical, medical and psychosocial benefits of exercise and appropriate (non-collision, non-contact) sports activities in haemophiliacs (9). By improving muscle strength, proprioception and joint health, dynamic, isokinetic and isometric exercises prevent joint displacement. Sports participation also facilitates social integration and adaptation, resulting in a better quality of life (10). The hemophilia community has sought to increase the recommended activity level of patients and to encourage participation in organized sports (11). The *Guidelines for the Management of Hemophilia*, published by the World Federation of Hemophilia (WFH), emphasize the importance of regular physical activity and that even contact sports or other activities classically viewed as dangerous can be enjoyed by hemophilic patients on proper prophylaxis. The sports typically recommended by the WFH include walking, golf, badminton, archery, cycling, rowing, sailing, and table tennis; however, high-contact and collision sports, such as soccer, boxing, wrestling, and hockey, may be considered on an individual basis (12). The choice of activity should reflect the individual's preference/interest, ability, physical condition and resources. Frequently children are not able to afford an adequate physical activity. To fix this problem, a study conducted by Wagner et al. established an online exercises program with the objective of let hemophiliac patients take part to regular training with correct instructions (13). Athletes with hemophilia should be accompanied in physical activities by trainers under the supervision of a Sports medicine physician. The evaluation allowing sport participation should be coordinated by an expert

on the field medical team and must include a haematological report. Adequate precautions must be taken by coaches and professional staff and the appropriate administration of prophylaxis as well as the treatment of any injury by including administration of the missing factor should be prearranged (14). The progressive spread of new long-acting recombinant factors could improve the accessibility to physical activities of haemophiliac patients (15). Unfortunately, Italian law regarding sports medicine certification to participate in organized sports, training and competition is unclear in the case of children with hemophilia (treated prophylactically). Two laws govern access to organized sport practice. The first (DM 18/02/1982 *Norme per la tutela sanitaria dell'attività sportive agonistica*) grant medical certification for competitive sports (16) and the second (DM 24/04/2013 *Disciplina della certificazione dell'attività sportiva non agonistica e amatoriale e linee guida sulla dotazione e l'utilizzo di defibrillatori semiautomatici e di eventuali altri dispositivi salva vita.*) for non-competitive sports (17). Certification for competitive sport is both sport- and age-related because is required for a systematic and constant amount of physical activity performed by an athlete within a Italian Olympic Committee structure and provides, eventually, the authorization for participation in Olympic Games. Consequently, the starting age for a competitive athlete is established by a National Sport Federation and the exams for competitive sports are annually performed: anthropometric evaluation, cardiological visit with electrocardiogram, oculist evaluation of visus oculi with colour recognition, spirometry and urine tests. I.e. for specific sports, such as swimming, hockey or rowing, athletes must have 10 years of starting age for competitive events and annual renewal of the certification. Participation in contact sports requires additional exams as neurological visit and audiometric tests. Given the specific requirements for participation in competitive sports, the certifier is exclusively a physician specialized in sports medicine (18). Non-competitive sports are played by student engaged in extracurricular sports or joined for fun or health purposes by general population. The participant does not aspire to the Olympic or World games. Certification for these types of activities can be obtained from doctors specialized in

sports medicine but also from family doctors (including paediatricians). Nonetheless, certification must be renewed annually, and the examination must include an electrocardiogram (16). Thus, in an observational single-center study, we investigated joint status before and after 12 months of organized physical activity in children with severe hemophilia managed by prophylaxis. The aim of this study was to determine whether those children may be eligible for competitive sport medical certification.

Materials and Methods

Study design

The study is a single-center, observational trial, consisting in periodical clinical assessment conducted at Pediatric Hemophilia Center, “Policlinico-Giovanni XXIII” Bari, Italy, during 12 month of a dedicated physical activity protocol based on HIITS (High Intensity Interval Training Sessions) performed at Sports Medicine Institute “Vito Accettura”, Bari.

Participants

Sixteen children aged between 3 and 15 y/o, with severe hemophilia (12 with HA and 4 with HB) with a mean starting prophylaxis age of $20,7 \pm 2,2$ months in accordance with the Hemophilia and Thrombosis Center, Pediatric Hemophilia Center, “Policlinico-Giovanni XXIII” Bari, Italy, were enrolled in the study from January 1st, 2016 to December 31st, 2016. Patients with mild-moderate hemophilia, a history of inhibitor developing or irreversible chronic arthropathy were excluded. All patients participated to the program for the entire duration the study. In our study, Canadian protocol has been used for the prophylaxis in the cohort. Children begun prophylaxis with a single weekly dose of 50 IU / kg. The bleeding frequency were evaluated every three months and the prophylaxis regimen were increased if the patient have bled three times since the last visit in the same joint or four times in total (passing firstly to 30 IU / Kg twice a week and then to 25 IU / Kg three times a week) (19). Signed informed consent were obtained from parents of every patient.

Procedure

The articular status of each patient was evaluated by a Radiologist Consultant according to the Hemophilia Joint Health Score 2.1 (HJHS) (20) and Haemophilia Early Arthropathy Detection with UltraSound (HEAD-US) (21) score before (T0) and after 12 months (T1) of a program of physical activity; all patients underwent a detailed hematological examination focusing on bleeding history and auxological parameters (weight, height, body mass index (BMI)). In addition, each patient was seen at the Pediatric Hemophilia Center, “Policlinico-Giovanni XXIII” Bari, Italy, where a clinical exam, audiometric test, ocular test, spirometry, electrocardiogram and cardiologic examination were performed in accordance with the requirements of Italian sports medicine certification. The National Hemophilia Foundation (NHF) published the dossier “Playing it Safe-Bleeding Disorders, Sports and Exercise” providing a sport associated risk level list. This classification guides patients for the choose of a physical activity according to their bleeding risk associated with haematological diseases (22). We assessed the frequency of accidental trauma occurring during physical activity, and we clinically assessed any skin and / or mucosal bleeding and ultrasound joint bleeding. We evaluated at T0 and T1, pressure, heart rate, saturation at rest and at the end of the session. All sessions were performed two times a week for one year: from 8 to 10 minutes of continuous physical activity with 30 second rest between two exercises. Programs consisted in 13 or 26 minutes of shuttle runs, jumping jacks, vertical jumps, mountain climbers, and plank in and out jumps; all sessions were preceded by a 10 minutes warm-up up including jogging and dynamic stretching (23).

Data Analysis

For each patient, data on weight, height, BMI and the articular parameters (HJHS and HEAD-US) of the joints were compiled. The data were analysed using the statistical software Stata/SE 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The values of the various joint parameters were compared using the MacNemar

test and the mean values using Student's t-test for paired samples. A p-value < 0.05 was considered to indicate statistical significance.

Results

Table 1 shows the characteristics of the 16 patients enrolled in this study. The median age at baseline was 5 years (range: 3–15). Twelve patients had severe HA and 4 patients severe HB. Ninety-six joints were evaluated in total. The results showed that after 12 months of sports participation both weight and height significantly increased, without an increase in the BMI, demonstrating the positive influence of physical activity for a correct development of the body (T0: mean \pm standard deviation 17.2 ± 3.2 ; T1: 18.7 ± 3.7 ; $p=0.03$, Tab. 1). The HJHS scores did not change significantly from T0 to T1 (T0: 1.6 ± 1 ; T1: 2.1 ± 1.3 ; $p>0.05$); there was a slight decrease in atrophy for the muscles of the right elbow (no atrophy seen at T0 in 4 of 16 patients and at T1 in 8 of 16 patients; $p=0.045$; Table 2). There was also no statistically significant worsening of the HEAD-US score at T1 of: synovium hypertrophy (ranging from absent to mild during the 12 months), cartilage (from normal to a loss of cartilage of at least 50%) and bone (normal to mild irregularities of the subchondral bone. Statistical comparison, using MacNemar test, revealed the absence of a statistically significant worsening of the HEAD-US scores in patients between T0 and T1 ($p>0.05$). Furthermore,

none of the patients developed injuries, skin or mucosal bleedings, cardiovascular or respiratory problems. Accordingly, all patients qualified for Italian competitive sport medical certification.

Discussion

Guidelines for sport participation for people with haemophilia were firstly stated by McLain and Helldrich (24) defining most appropriate sport for this category of patients, published in 2002. Successively, NHF accepted those statement supporting this classification. Admission for patients with haemophilia to sport events or obtain competitive sport medical certification is an obstacle course. In US, i.e. the ADA (25), is a statute that for years, did not clarified if people with haemophilia should be eligible for sport participation. Only in 2008, were clarified that people with haemophilia are included in the statute (26). One of the first athletes that participate several sport events with a diagnosed Christmas Diseases (Haemophilia B), was a hockey player, who struggled against medical committee to persist his competitive career in 1980 (27). In past years, several studies were conducted to assess the level of sport participation of people with haemophilia. It's evident that a wide range of sports is very accessible to people with haemophilia, such as swim, running, soccer, volleyball, cardio-fitness and gymnastic, without life-threatening or even mild bleeding episodes, coupled to a correct prophylaxis

Table 1. Auxological parameters and joint characteristics at T0 and T1. T: Time Point; SD: Standard Deviation; IQR: Interquartile range; t: Student's t test; BMI: Body Mass Index; HJHS: Hemophilia Joint Health Score.

| | T | Mean | SD | Range | | Median | IQR | | t | p |
|------------------|----|-------|------|-------|-------|--------|-------|-------|-----|---------|
| Weight | T0 | 30,7 | 18,4 | 10,0 | 68,8 | 23,0 | 16,0 | 45,0 | 8,9 | <0,0001 |
| | T1 | 34,6 | 19,5 | 11,5 | 72,0 | 28,0 | 18,0 | 51,0 | | |
| Height | T0 | 124,9 | 24,7 | 87,0 | 174,0 | 123,0 | 105,0 | 143,5 | 6,1 | <0,0001 |
| | T1 | 129,7 | 25,4 | 92,5 | 178,0 | 128,5 | 109,0 | 149,5 | | |
| BMI | T0 | 17,2 | 3,2 | 12,8 | 22,7 | 16,7 | 14,5 | 20,3 | 2,5 | 0,03 |
| | T1 | 18,7 | 3,7 | 13,4 | 26,5 | 18,0 | 15,8 | 21,8 | | |
| HJHS Total Score | T0 | 1,6 | 1,0 | 0,0 | 4,0 | 2,0 | 1,0 | 2,0 | 1,5 | 0.1 |
| | T1 | 2,1 | 1,3 | 0,0 | 4,0 | 2,0 | 1,0 | 3,0 | | |

Table 2. HJHS. Muscle atrophy; n=number of patients.

| Joint | | T0 | | T1 | | MacNemar χ^2 | p |
|-------------|--------|------|------|------|------|----------------------|--------------|
| | | n | % | n | % | | |
| Left elbow | none | 14,0 | 87,5 | 11,0 | 68,8 | 3,0 | 0,08 |
| | mild | 2,0 | 12,5 | 5,0 | 31,2 | | |
| | severe | 0,0 | 0,0 | 0,0 | 0,0 | | |
| Right elbow | none | 4,0 | 25,0 | 8,0 | 50,0 | 4,0 | 0,045 |
| | mild | 12,0 | 75,0 | 8,0 | 50,0 | | |
| | severe | 0,0 | 0,0 | 0,0 | 0,0 | | |
| Left knee | none | 11,0 | 68,8 | 10,0 | 62,5 | 0,3 | 0,56 |
| | mild | 5,0 | 31,2 | 6,0 | 37,5 | | |
| | severe | 0,0 | 0,0 | 0,0 | 0,0 | | |
| Right knee | none | 11,0 | 68,8 | 8,0 | 50,0 | 1,8 | 0,18 |
| | mild | 5,0 | 31,2 | 8,0 | 50,0 | | |
| | severe | 0,0 | 0,0 | 0,0 | 0,0 | | |
| Left ankle | none | 15,0 | 93,7 | 14,0 | 87,5 | 1,0 | 0,32 |
| | mild | 1,0 | 6,3 | 2,0 | 12,5 | | |
| | severe | 0,0 | 0,0 | 0,0 | 0,0 | | |
| Right ankle | none | 15,0 | 93,7 | 14,0 | 87,5 | 1,0 | 0,32 |
| | mild | 1,0 | 6,3 | 2,0 | 12,5 | | |
| | severe | 0,0 | 0,0 | 0,0 | 0,0 | | |

(28, 29, 30) and that even if hemophilia is a disabling disease, it does not prevent from a healthy and active lifestyle (31). Our study is the first in Italy that investigates whether children receiving prophylaxis for severe hemophilia are eligible for competitive sport medical certification. It is also the first step in achieving legislative recognition for competitive/non-competitive certification for children with haemophilia, that is an evident gap detectable in Italian law (16). In our study, we observed that despite absence of specific recommendations about hemophiliacs, prophylactically treated young patients are capable to obtain a regular certification for sport participation. In Italy, participation to competitive or non-competitive sport activities is regulated by health prevention laws that make medical visits as mandatory, requiring annual renewal with specific tests depending on type of certification (competitive or non competitive) (16, 17). In 2013, has been stated that in the event of suspected diagnosis or in the presence of chronic and full-blown pathologies, the certifying doctor is recommended to seek the

advice of the sports medicine and, according to clinical judgment, the branch specialist for the final release of the certification (17). The “state of good health” is certified within the diagnostic limits of the tests carried out and that the certification does not imply any judgment of suitability for a specific sport, unlike the Certificate of competitive fitness. Currently there are no laws regulating the acquisition of a competitive and non-competitive sports certification for haemophiliac patients, this happens for other conditions i.e. for diabetes mellitus (32). Among the limitations of our observational study, there are the design as a single-institution study, the small sample size and the short observation time. In our study we have shown that children with severe hemophilia could obtain competitive medical-sports certification because, with current prophylactic protocols, they may not have deficits that would hinder the obtaining of certification. Italian law does not provide for any evaluation protocol for hemophilia patients and the evaluation is carried out by the sports specialist. For this reason, the hematologist

should be consulted for a complete evaluation of the hemophilic patient. Furthermore, none of the children in our study showed clinical or radiological evidence of an impaired articular status after one year of activity. Finally, the observed reduction in the atrophy of the dominant arm, as an indicator of improved physical fitness, further suggests that regular physical activity improves self-esteem. The certification of eligibility to participate in sports should be periodically renewed. Has been commonly stated by several recent studies that children with hemophilia are less physically fit with a higher incidence of obesity and (33, 34, 35) predisposed to development fractures and increased incidence of osteoporosis in adult age due to significant lower bone density as well (36). Furthermore, the choice of the type of activity should be guided by the physician and but experts in the field of prevention. Ross et al. (2009), conducted a study determining the influence of different impact level sport on the wellness of haemophiliac patients joints and associated bleeding risk (37). With a correct prophylaxis protocol, patients conducting a high impact regular physical activity exhibited > 1 bleeding episodes per training season. This should represent barriers eliminating factor to patients with haemophilia, in particular children. All those aspects strengthen the crucial role of physical activity on children with haemophilia. Screening is a tool to prevent age associated diseases such as cardiovascular impairment directly associated to a sedentary lifestyle and indirectly associated to haemophilia (38).

Conclusions

While sports participation seems to be an effective collateral therapy in patients with hemophilia, for the certifying physician the decision regarding the permissible type of sport may pose a dilemma. However, the decision will depend on the individual patient, his clinical history and the specific aspects of the sport. Since the potential for physical injury is the same in competitive and non-competitive sports, the risk evaluation for the patient with hemophilia must take into account other variables, including disease severity, therapeutic program, comorbidities and complications, joint status, type of sport, locations of the competitions and the type

of health personnel present during events or training. Therefore, the clinical assessment should be performed by a physician specialized in bleeding disorders and by a sports medicine doctor. Analogous to other chronic diseases (for example, juvenile diabetes) the physician specialized in bleeding disorders should prepare a report on the patient's clinical history and submit it to the sports medicine doctor before the latter determines whether the patient is eligible to participate in non-competitive vs. competitive sports based on physical ability, bleeding risk, previous experience and the attitude of caregivers, particularly the patient's parents. There are still many steps to be taken before sports participation by children with hemophilia becomes widely accepted, but meetings between the scientific community, patients' associations and other stakeholders are currently ongoing and expected to be productive (17). Finally, co-existence of the therapy with sport participation might be better managed in the future thanks to cost benefits analysis assessing the capacity of primary prophylaxis to improve quality of life compared to on-demand therapy (39) and thanks to results about available extended half-life molecules and favorable results in gene therapy that should result in a definitive cure (40, 41).

List of Abbreviations: Deficiency of coagulation factor VIII (HA), Deficiency of coagulation factor IX (HB), Von Willebrand factor (VWF), World Federation of Hemophilia (WFH), Hemophilia Health Joint Score 2.1 (HJHS), Ultrasound HEAD-US Score (HEAD-US).

Ethics approval and consent to participate: The patients' parents provided written informed consent for their children's participation in the study.

Consent for publication: The patients' parents provided written informed consent for data publication.

Data availability statement: The datasets used in this study and the results of the analyses are available from the corresponding author upon reasonable request.

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