American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:158–167 (2017)

ARTICLE

The Evidence-Based Rationale for Physical Therapy Treatment of Children, Adolescents, and Adults Diagnosed With Joint Hypermobility Syndrome/Hypermobile Ehlers Danlos Syndrome

RAOUL H.H. ENGELBERT,* BIRGIT JUUL-KRISTENSEN, VERITY PACEY, INGE DE WANDELE, SANDY SMEENK, NICOLETA WOINAROSKY, STEPHANIE SABO, MARK C. SCHEPER, LESLIE RUSSEK, AND JANE V. SIMMONDS

New insights into the phenotype of Joint Hypermobility Syndrome (JHS) and Ehlers-Danlos Syndrome-hypermobile type (hEDS) have raised many issues in relation to classification, diagnosis, assessment, and treatment. Within the multidisciplinary team, physical therapy plays a central role in management of individuals with hypermobility related disorders. However, many physical therapists are not familiar with the diagnostic criteria, prevalence, common clinical presentation, and management. This guideline aims to provide practitioners with the state of the art regarding the assessment and management of children, adolescents, and adults with JHS/hEDS. Due to the complexity of the symptoms in the profile of JHS/hEDS, the International Classification of Functioning, Disability and Health (ICF) is adopted as a central framework whereby the umbrella

Dr. Jane Simmonds is Chair of the International Ehlers Danlos Syndrome Physical Therapy Clinical Guidelines working group. She is a Senior Teaching Fellow at Great Ormond Street Institute of Child Health, University College London and clinical lead in the Hypermobility Unit at the Hospital of St John and St Elizabeth in London. Jane is an active researcher and has more than 20 years of clinical experience working with this patient group. She is physiotherapy advisor to three UK patient charities and has published widely and presents regularly at international conferences in the field of hypermobility, bone health and Ehlers Danlos Syndrome.

Prof. Raoul Engelbert is Professor of Physiotherapy at the University of Amsterdam (AMC) where focussing on transition of care in complex patients. He is the Director of Research, Center of Research ACHIEVE, Faculty of Health, University of Applied Sciences Amsterdam and has researched for over two decades and published widely in the field of heritable disorders of connective tissue, hypermobility and Ehlers Danlos Syndrome.

Professor Birgit Juul Kristensen is Associate Professor, Research Unit of Musculoskeletal Function and Physiotherapy, University of Southern Denmark, and Professor at the Institute of Occupational Therapy, Physiotherapy and Radiography, Bergen University College, Norway. She is an active researcher and has published widely in the field of musculoskeletal dysfunction and hypermobility.

Dr. Verity Pacey is a Senior Lecturer in the Department of Health Professions, Macquarie University, and Senior Physiotherapist at The Children's Hospital at Westmead, with over 10 years clinical and research experience working with children and adolescents with symptomatic hypermobility. Verity's research focuses on the assessment, treatment and quality of life of children and adolescents with connective tissue disorders.

Dr. Inge De Wandele is a physiotherapist at the Center for Medical Genetics at Ghent University Hospital, Belgium. The topic of her PhD was the presence of dysautonomia in EDS. Her current clinical work and research focus on adapted physiotherapy for patients with heritable connective tissue disorders and generalized joint hypermobility.

Stephanie Sabo is a senior physical therapist who practices in outpatient developmental paediatrics evaluating and treating infants, children and adolescents. She is the leader of the Joint Hypermobility Evidence Based Practice Team at Cincinnati Children's Hospital Medical Center. She has also participated in program developmental for an intensive based therapy program for children with Joint Hypermobility Syndrome and EDS. She is involvement in multiple research studies that relate to intensive therapy services and patients with EDS/Hypermobility.

Nicoleta Woinarosky is a Health Resource Consultant for the Improving the Life of Children and Families Foundation (ILC), Nicoleta draws on her education (Master's thesis on The Effects of Exercise/Physical Activity on Chronic Pain and Pain Related Mental Health Issues), volunteer work (teaching chronic pain self-management and physical education to seniors), and experience (living with EDS and chronic pain) to provide evidence-based information to health professionals and persons living with chronic pain syndromes including EDS. While recognizing the need for pain medications, she is passionate about the physical and psychological benefits of exercise.

Sandy Smeenk is the co-Founder and Executive Director of the Improving the Lives of Children and Families with Chronic Pain Charitable Foundation ("ILC"), a national charity catalyzing efforts to address the burden of pain through evidence-based awareness and education, systems change and knowledge translation. She has led substantiate initiatives to influence Ministry of Health mandated programs for people with rare diseases utilizing Ehlers-Danlos Syndrome (EDS) as a model of optimal care.

Mark Scheper is a physiotherapist and clinical movement scientist. Currently working as a senior lecturer physiotherapy at the University of Applied sciences Amsterdam and a researcher affiliated to the Academic Medical Center Amsterdam, department of rehabilitation. His current research focus is on disability and chronicity in children with chronic diseases, with special attention for diseases of connective tissue.

Dr. Leslie Russek is an Associate Professor teaching musculoskeletal physical therapy and research courses in the Clarkson University Doctor of Physical Therapy program. She has been researching hypermobility syndrome for almost 20 years, and treats patients in her areas of specialty: hypermobility, fibromyalgia, and headaches.

*Correspondence to: Prof. Raoul H.H. Engelbert, ACHIEVE, Centre for Applied Research, Education of Physiotherapy, Faculty of Health, University of Applied Sciences Amsterdam, Amsterdam, The Netherlands. E-mail: r.h.h.engelbert@hva.nl

DOI 10.1002/ajmg.c.31545

Article first published online in Wiley Online Library (wileyonlinelibrary.com).

term of disability is used to encompass functions, activities and participation, as well as environmental and personal factors. The current evidence-based literature regarding the management of JHS/hEDS is limited in size and quality and there is insufficient research exploring the clinical outcomes of a number of interventions. Multicenter randomized controlled trials are warranted to assess the clinical and cost-effectiveness of interventions for children and adults. Until further multicenter trials are conducted, clinical decision-making should be based on theoretical and the current limited research evidence. For all individuals diagnosed with JHS/hEDS, international consensus and combined efforts to identify risk profiles would create a better understanding of the pathological mechanisms and the potential for optimizing health care for affected individuals.

KEY WORDS: physical therapy; diagnostics; treatment; guidelines; joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome; international classification of functioning

How to cite this article: Engelbert RH, Juul-Kristensen B, Pacey V, de Wandele I, Smeenk S, Woinarosky N, Sabo S, Scheper MC, Russek L, Simmonds JV. 2017. The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome. Am J Med Genet Part C Semin Med Genet 175C:158–167.

INTRODUCTION

In the last decade, scientific research in the area of hypermobility related disorders has grown. Scientific exploration has not only provided new insights into the phenotype of Joint Hypermobility Syndrome (JHS) and Ehlers-Danlos Syndrome-hypermobility type (hEDS), but it has also raised many issues in relation to classification, diagnosis, assessment, and treatment. We will refer to these overlapping/indistinguishable clinical entities [Tinkle et al., 2009; Remvig et al., 2011], in this paper as JHS/hEDS. Within the multidisciplinary team, physical therapy plays a central role in management of individuals with hypermobility related disorders [Simmonds and Keer, 2007; Grahame and Hakim, 2008; Scheper et al., 2013, 2016a]. The reported prevalence of JHS/hEDS in adult physical therapy outpatient musculoskeletal settings has been reported to be between 30% [Connelly et al., 2015] and 55% [Clarke and Simmonds, 2011]. Despite the relatively high incidence of JHS/hEDS, recent research has found that many physical therapists and other clinicians are not familiar with the diagnostic criteria, prevalence, or common clinical presentation of affected individuals [Billings et al., 2015; Lyell et al., 2016; Russek et al., 2016], whereas clinicians also experience a lack of awareness of this condition [Billings et al., 2015; Rombaut et al., 2015a; Terry et al., 2015; Lyell et al., 2016]. This guideline aims to provide physical therapists and other clinicians with the state of the art regarding the assessment and management of children, adolescents, and adults with JHS/hEDS. In preparing the guideline, the quality of evidence is graded according to the GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation) [Balshem et al., 2011]. The paper has been written based on a synthesis of best evidence available and consensus opinion of an international group of researchers, clinicians, and patient representatives. Evidenced-based assessment and treatment strategies should be used where available. In the absence of these, therapists should be guided by clinical reasoning and assessment and treatment should be tailored to the individual patient's needs.

Due to the complexity of the symptoms in the profile of JHS/hEDS, the International Classification of Functioning, Disability and Health (ICF) is adopted as an overarching framework [Atkinson and Nixon-Cave, 2011]. Disability, according to the World Health Organization, is an umbrella term covering functions, activities and participation, as well as environmental and personal factors [WHO, 2015]. In children, adolescents and adults with JHS/hEDS, impairments in the ICF domain body and function may result in decreased functional capacity and restrictions in participation.

The Beighton tests for assessing generalized joint hypermobility (GJH) are widely used and were described about 40 years ago, but only with photos and unclear legends accompanying [Beighton et al., 1973]. Considerable variation exists in the utilization of this tool, the cut-off level used for a positive test and in the criteria definition of GJH [Remvig et al., 2007]. The Beighton score, consisting of five clinical maneuvers, is scored dichotomously (0/1) from which a total score, ranging from 0 to 9, is calculated. It is a widespread belief that GJH is present in adults with a Beighton score of $\geq$4 as described in the diagnostic Brighton criteria [Grahame et al., 2000] and for hEDS $\geq$5 [Beighton et al., 1998]. Other cut-off points for detecting the presence of GJH have been proposed, especially for children, among others $\geq$6, $\geq$7, and $\geq$8 [Jansson et al., 2004]. Although these testing procedures and diagnostic criteria have been in place for years and are considered the gold standard from infancy to old age [Adib et al., 2005], criticism has arisen from clinicians and researchers about its diagnostic and clinical usefulness and predictive validity [Juul-Kristensen et al., 2017]. Beyond the Beighton scale, other assessment measures should be utilized within each domain of the ICF and clinical reasoning should underpin where appropriate, and where possible evidence-based, tailored treatment strategy.

Beyond the Beighton scale, other assessment measures should be utilized within each domain of the ICF and clinical reasoning should underpin where appropriate,

and where possible evidence-based, tailored treatment strategy.

JHS/hEDS IN CHILDHOOD

Children with JHS/hEDS may experience multiple impairments as a result of increased laxity of the connective tissues, incorporating complaints in all domains of the ICF as illustrated in Figure 1 [Pacey, 2014].

Pain and Health Related Quality of Life

In JHS/hEDS pain is often present. It is not known why some children develop pain and other symptoms, while others do not. The primary hypothesis regarding the development of musculoskeletal complaints is localized biomechanical overload during activity, with a high risk of repetitive trauma. Generalized joint instability may cause the occurrence of micro-traumas in joint surfaces, leading toward adaptation and compensation of movement patterns, consequently causing overload in other areas of the musculoskeletal system [Ferrell et al., 2004]. Pain exacerbated by activity is a distinguishing feature of JHS/hEDS. Eighty-one percent of children with JHS attending a rheumatology service reported that their pain was exacerbated by exercise [Adib et al., 2005]. All of these children reported experiencing pain in the 24 hr following exercise: 65% immediately post exercise, 59% later that evening, and 50% the following morning. The knee, a weight-bearing joint of the lower limb, and the shoulder, are the most commonly affected sites of pain in children with JHS/hEDS [Adib et al., 2005; Pacey et al., 2015a]. Parent and child self-reported pain intensity is highly correlated [Pacey et al., 2015b], although parents have been shown to underestimate their child's perception of pain [Kemp et al., 2010]. Recently it was shown that children and adults diagnosed with JHS/hEDS are not only characterized by GJH, and chronic pain, but also by the presence of generalized hyperalgesia (GHA) [Scheper et al., 2016b]. The presence of GHA may indicate involvement of the central nervous system in the development of chronic pain and may not only provide insights as to the phenotype of GJH related disorders, but also indicates diagnostic qualities that may be useful in clinical practice [Scheper et al., 2016c].

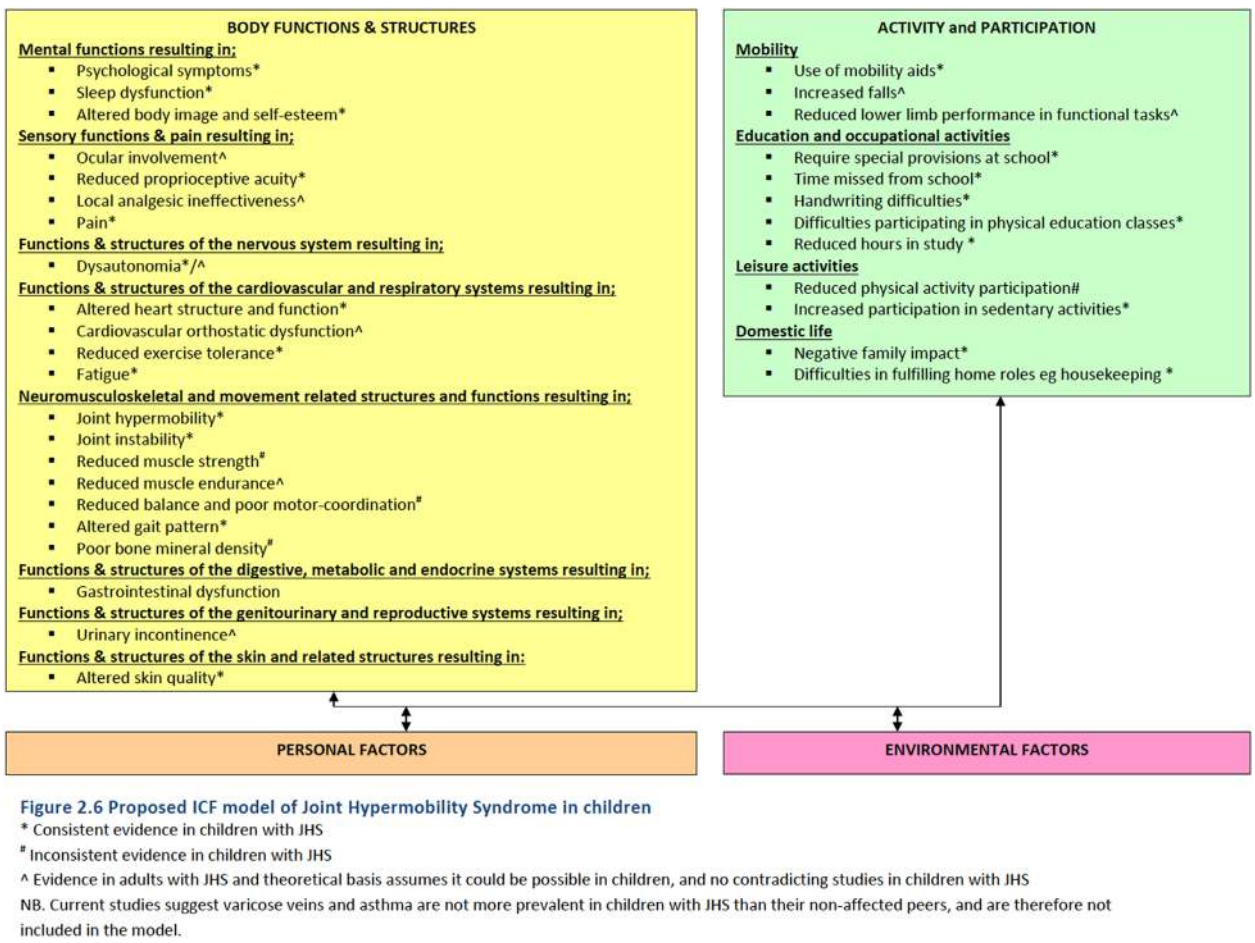

Figure 1. Proposed ICF model for JHS in children by Pacey [2014].

Children aged 9–12 years old with JHS/hEDS and knee pain report lower Health Related Quality of Life (HRQL) than healthy children at the same age [El-Metwally et al., 2005; Fatoye et al., 2011]. Children with JHS/hEDS experience poor HRQL and disabling fatigue, with parent scores providing a good proxy. Pain, fatigue, and the presence of stress incontinence symptoms have been demonstrated to have the greatest impact on their HRQL [Pacey et al., 2015a].

Dysfunction in JHS/hEDS can be the result of chronic pain but also due to involvement of multiple systems, psychological distress and related disability. How chronic pain and systemic deficits come into effect and interact with each other is currently unknown. The specific problems related to the GJH related syndromes as compared with other chronic pain syndromes are still challenging for most clinicians and scientists due to many issues surrounding etiology, disease classification, diagnostics, and treatment [Scheper et al., 2015].

Proprioception, Muscle Strength, and Balance

Another important factor within the biomechanical pathway in JHS/hEDS patients may be reduced proprioceptive acuity, which has been suggested to be important for the occurrence of gait abnormalities and musculoskeletal pain [Smith et al., 2013]. Decreased knee joint proprioception in combination with decreased knee flexor and extensor muscle strength has also been reported in children with JHS/hEDS [Fatoye et al., 2009]. This was partly confirmed in another study of adolescents and adults with JHS/hEDS where the reflex in the knee extensors was absent in 47% of 15 patients, compared with a healthy control group in which this reflex was present in all subjects [Ferrell et al., 2007]. Decreased muscle strength is associated with activity limitations in JHS/hEDS patients. Joint proprioception has been found to influence this association and should be considered in the development of new treatment strategies for patients with JHS/hEDS [Scheper et al., 2016a]. Children between 8 and 16 years of age with JHS/hEDS assessed by the balance subsection of the Bruininks–Oseretsky test of motor proficiency (2nd edition), have been found to have significantly reduced balance [Schubert-Hajlmarsson et al., 2012].

Decreased muscle strength is associated with activity limitations in JHS/hEDS patients. Joint proprioception has been found to influence this association and should be considered in the development of new treatment strategies for patients with JHS/hEDS.

Joint Instability

Dislocations or subluxations in more than one joint, or in one joint on more than one occasion, form part of the diagnostic criteria for JHS/hEDS. Consequently, recurrent joint instability episodes are commonly reported by children with JHS/hEDS, with the knee, ankle, and shoulder as the most affected joints [Pacey et al., 2015b].

Extra-Articular Features

In children with JHS/hEDS involvement of not only the skin and joints but also other organ systems consisting of different types of collagen, for example, bone and blood vessels, indicates a more systemic rather than local involvement. In children 8–9 years old with JHS/hEDS, lower ultrasound values in bone, higher degradation products in urine, higher skin extensibility, and lower blood pressure have been observed in comparison with a non-symptomatic hypermobile group [Engelbert et al., 2003]. High levels of urinary incontinence are reported in children with JHS/hEDS [Pacey et al., 2015a], where such systemic concerns cause significant discomfort and impacts significantly on function and quality of life, a referral to a pediatrician or system specialist is required [de Kort et al., 2003].

A relationship between JHS/hEDS and a characteristic neurodevelopmental profile affecting coordination is emerging. Common symptoms shared between children with JHS/hEDS and those with developmental coordination disorder (DCD) have been highlighted [Kirby and Davies, 2007]. Multiple clinical features of JHS/hEDS, such as "double-jointedness," joint pain, flat feet, easy bruising and dysautonomic symptoms, have been found to be significantly more frequent in children with DCD than in children without [Kirby and Davies, 2007]. Among children with JHS presenting to health care services, 36% report poor coordination and 48% report clumsiness, and problems with gait, falls, and coordination are the second most common presenting complaint [Adib et al., 2005]. Overall gross motor abilities have been shown to be reduced in 22% of children (mean 8 years of age) with JHS/hEDS measured with the Movement Assessment Battery for Children [Hanewinkel-van Kleef et al., 2009].

Symptoms of gastrointestinal dysfunction (GID) and dysautonomia may commence very early in a child's life. The most common GID symptoms include gastrointestinal reflux, abdominal pain, and slow transit constipation or long standing intractable diarrhea; however, abnormalities from the mouth to the anus have been reported [Abonia et al., 2013].

Psychological Symptoms

Children and adolescents with JHS/hEDS aged 8–15 years report significantly poorer emotional functioning on the Pediatric Quality of Life Inventory compared to their non-hypermobile peers [Pacey et al., 2015b]. Furthermore, self-esteem, behavior, and psychosocial functioning of children with JHS/hEDS have been shown to be significantly lower than population norms prior to commencing a treatment program [Pacey et al., 2013].

Activities: Motor Development, Gait Pattern, Physical Fitness

The medical history often reveals developmental delay during early childhood and DCD may coexist [Kirby et al., 2005; Kirby and Davies, 2007]. Congenital hypotonia or "floppy infant" syndrome and joint hypermobility (JH) have been recognized by a number of researchers [Mintz-Itkin et al., 2009]. Late walking and clumsiness are characteristics commonly reported by parents [Adib et al., 2005]. In JHS/hEDS, non-physiological gait-patterns (absolute comparisons: spatio-temporal, kinematics, and kinetics) have been demonstrated in children. These patterns were not consistent and a high variability within patients was present [Fatoye et al., 2011], and children with JHS/hEDS and multiple joint pain, had significantly decreased knee flexion in the swing phase, as well as increased knee extension in mid-stance during walking. Also, decreased lateral joint stability and different stabilization strategies (kinetic patterns) in children and adults with GJH have been shown [Falkerslev et al., 2013].

As far as the gait pattern of children with JHS/hEDS is concerned, it has been reported that "hypermobile joints, reduced proprioception, weak muscles, and reduced stamina (endurance) can profoundly affect the gait of a child with JHS/hEDS. To correct this, the causes of the abnormalities need to be identified and worked on separately, before the gait will improve" [Murray, 2006]. Problems with gait, falls and coordination are the second most common presenting complaint of children with JHS/hEDS presenting to an outpatient rheumatology clinic [Adib et al., 2005].

In children with JHS/hEDS, a relationship was found with exercise induced pain and reduced aerobic fitness and physical capacity fitness compared with a healthy reference group, measured as absolute and relative (related to body mass) peak VO_2 [Engelbert et al., 2006], and also when assessed with a sub-maximal 6 min walk test [Hanewinkel-van Kleef et al., 2009]. The reason for this poor aerobic fitness was assumed to be due to musculoskeletal pain, resulting in inactivity and deconditioning, which could then result in exercise-induced pain and intolerance.

Participation: Hobbies, Sport, and Social Activities

Children with GJH are less active in sports and miss education more often in comparison with their healthy peers with normal joint mobility [Jansson et al., 2004]. Qualitative research with children with JHS/hEDS and their parents has identified "difficulties at school" as being one of the six main themes, when discussing symptoms prior to commencing a treatment program [Birt et al., 2014]. A retrospective chart audit also showed that 40% of affected children report handwriting difficulties, 24% report "problems at school," 41% report missing time from school, and 48% were unable to participate in physical education classes as a result of their condition [Adib et al., 2005]. A recent study showed that children 8–16 years with JHS/hEDS had significantly decreased participation in housework, riding a bicycle, taking part in sport or outdoor games, as assessed by the Frequency of Participation Questionnaire, in conjunction with a higher frequency of participation in non-sporting games and a higher need to rest [Schubert-Hajlmarsson et al., 2012]. Withdrawal from physical activity due to their condition has also been reported by children and their parents [Birt et al., 2014].

Qualitative research with children with JHS/hEDS and their parents has identified "difficulties at school" as being one of the six main themes, when discussing symptoms prior to commencing a treatment program.

It is essential therefore for clinicians to explore and understand the impact of the child's problems on school, home and social life. Some children have poor school attendance records due to recurrent injury, pain, and systemic issues. Many children reduce physical activity and stop participating in physical education due to fear of re-injury or pain.

Finding out about hobbies, ambitions, and sports that a child enjoys is very helpful in driving the management plan. Physical therapists and parents have difficulty when searching for sports and hobbies that suit the child, because many sports involve movement or activities with high risk of injuries in unstable joints. Contact sports for example have been suggested to be an injury risk factor for knee injuries amongst individuals with GJH [Pacey et al., 2010]. In reality many children with JHS/hEDS cannot keep participating in their preferred hobbies, sports and activities, despite their hypermobility originally being considered an asset. It can therefore be very challenging to find activities which young people like and which do not exacerbate pain and joint instability

JHS/EDS-HT IN ADULTHOOD

Pain, Fatigue, and Health Related Quality of Life

Adults diagnosed with JHS/hEDS often experience joint pain in multiple joints, which can vary from localized to widespread pain, in nature and severity [Remvig et al., 2011; Connelly et al., 2015]. Chronic widespread pain is frequently present in patients with the JHS/hEDS. In half of the patient group, a predominantly neuropathic pain component was present [Rombaut et al., 2011a]. This study provides evidence for the existence of hyperalgesia even in asymptomatic areas (generalized secondary hyperalgesia). The GHA (generalised

hyperalgesia) may represent the involvement of a sensitized central nervous system, which requires an adapted pain management approach for this patient group [Rombaut et al., 2015b].

Fatigue symptoms are heterogeneous in nature and can vary from mild to severe. However, patients often report fatigue symptoms as the most disabling complaint. In addition, neurologically oriented symptoms (proprioceptive deficits, central mediated hyperalgesia), psychological dysfunction (anxiety, depression), and systemic complaints (organ dysfunction, dysautonomia) are often highly prevalent in JHS/hEDS [Voermans and Knoop, 2011; De Paepe and Malfait, 2012].

Fatigue symptoms are heterogeneous in nature and can vary from mild to severe. However, patients often report fatigue symptoms as the most disabling complaint.

Muscle Strength, Proprioception, and Balance

Rombaut et al. [2012] demonstrated severely reduced quantitative muscle function and impairment in physical function in patients with JHS/hEDS compared to age- and sex-matched controls. The muscle weakness may be due to muscle dysfunction rather than reduced muscle mass. Whether muscle strength and endurance can be improved by appropriate exercise programs needs evaluation in further studies. Compared with healthy participants, individuals with JHS/hEDS showed significantly impaired balance, reflected by increased sway velocity, mediolateral and anteroposterior sway excursion, and sway area during modified Clinical Test of Sensory Interaction on Balance (mCTSIB) and the Tandem Stance test (TS). Gait velocity, step length, and stride length were significantly smaller during all walking conditions, and a significant dual-task-related decrement was found for gait velocity, step and stride length, and cadence in the JHS/hEDS subjects compared with the control group. Ninety-five percent of the patients fell during the past year, and some fear of falling was further measured [Rombaut et al., 2011b]. DCD may persist into adulthood. In a case control study, 56% of those with JHS/EDS-HT met the criteria for adult DCD [Clark et al., 2014]. Proprioception has been shown to be impaired in a number of studies [Smith et al., 2013].

Extra-Articular Features

Dysautonomia, defined as a term for various conditions in which the autonomic nervous system does not work correctly, provides a complex challenge for the multidisciplinary team. Dysautonomia consisting of cardiovascular dysfunction is found to be present in JHS/hEDS. Neuropathy, connective tissue laxity, and vasoactive medication are likely to play a role in its development [De Wandele et al., 2014]. Gastrointestinal symptoms are also commonly reported [Zarate et al., 2010], impact significantly on quality of life and are managed in a variety of ways. Specialist medical referral may be necessary. Constipation requires active treatment usually including dietary advice, however sustained use of laxatives is often required. Adult women with JHS/hEDS have an increased rate of incontinence. Both case-control and cross-sectional studies consistently report that 60–73.3% of adult women with JHS/hEDS have urinary incontinence, compared with only 30–48.3% in non-affected women [Mastoroudes et al., 2013]. The increased rate seen in women with JHS/hEDS is present with various types of incontinence, including urgency incontinence, nocturnal enuresis, and intercourse incontinence [Nijs et al., 2000]. Other symptoms of lower urinary tract dysfunction including nocturia (waking one or more times at night to void), urgency, bladder pain, urinary tract infections, and voiding difficulties (poor stream, straining, incomplete bladder emptying, postmicturition dribble) have also been reported to be significantly more prevalent in women with JHS/hEDS [Mastoroudes et al., 2013]. No studies have yet investigated incontinence or other lower urinary tract symptoms in adult men with JHS/hEDS.

Impaired bone health in adults with JHS/hEDS has been demonstrated by significant reductions in volumetric bone density measured at the distal radius site using peripheral quantitative computed tomography in comparison with age and gender matched peers [Nijs et al., 2000]. However, in contrast Carbone et al. [2000] found that after correction for height, weight, and amount of physical activity, no significant differences between bone density measured by dual energy absorptiometry was found in adults with JHS/hEDS and controls.

Activities and Participation

Significant disability has been shown in patients with JHS/hEDS in ambulation (walking, running, stair climbing), activities of daily living (personal hygiene, self-care) and sports activities, influencing quality of life. The high number and severity of complaints in JHS/hEDS result in substantial care and treatment seeking. In a group of 78 adults with JHS/hEDS registered as patients in a rehabilitation medicine department, 92.4% were medication consumers, 70.9% had underwent several surgical interventions, and 51.9% had received physiotherapy treatment [Rombaut et al., 2011a]. The main objective of rehabilitation is to reduce disability and to improve quality of life, however, evidence concerning effectiveness of treatment for reducing disability is limited, as are the actual factors related to disability. A recent meta-analysis showed that pain, fatigue, and psychological distress had a significant impact on disability [Scheper et al., 2016b].

Psychological Symptoms

A systematic review has demonstrated that compared with their non-affected peers, adults with JHS/hEDS have

greater risk of anxiety, depression and panic disorders [Smith et al., 2014a]. A nationwide population-based cohort study showed a high incidence of psychiatric disorders including anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorder in the JHS/hEDS patient population [Cederlöf et al., 2016].

PRINCIPLES OF MANAGEMENT OF INDIVIDUALS WITH JHS/EDS-HT IN CHILDHOOD, ADOLESCENCE, AND ADULTHOOD

In children and adults with JHS/hEDS with symptomatic joints or intestinal and systemic problems, differential diagnostics have to be performed to exclude other diseases or disorders that are characterized by GJH. In individuals with GJH, easy bruising and frequent fracturing, the presence of a collagen disease such as osteogenesis imperfecta or osteopenia due to vitamin D deficiency should be considered. When GJH and musculoskeletal complaints as well as a Marfanoid habitus is present, Marfan or Loeys-Dietz syndrome should be considered. Severe collagen diseases, such as the other types of EDS should be excluded. In case of progressive muscle weakness central of peripheral neurological conditions including myopathies should be ruled out. Additionally, rheumatology conditions should also be considered and ruled out.

Kemp et al. [2010] performed the first prospective randomized controlled trial (RCT) in children comparing a 6-week generalized program, improving muscular strength and fitness, with a targeted program aimed at correcting motion control of symptomatic joints. It was demonstrated in 57 children that significant improvements in both the children's and parental pain scores were reached in both groups. A recent RCT study of children with JHS/hEDS and hypermobile knees found an increased effect on psychosocial/self-esteem in the group that performed knee exercises into the hypermobile range of motion (ROM) compared with the control group performing knee exercises into neutral ROM. Both groups improved knee strength and reduced knee pain [Pacey et al., 2013]. Evidence-based guidelines suggest that children with flexible flat foot presenting with pain or impaired function, particularly in the presence of GJH, such as that commonly seen in children with JHS/hEDS, should use orthotics and/or sensible footwear [Evans and Rome, 2011]. Preliminary findings of a small RCT suggests that use of orthotics may improve the efficiency of gait of children with GJH and DCD [Morrison et al., 2013].

Kemp et al. performed the first prospective randomized controlled trial (RCT) in children comparing a 6-week generalized program, improving muscular strength and fitness, with a targeted program aimed at correcting motion control of symptomatic joints. It was demonstrated in 57 children that significant improvements in both the children's and parental pain scores were reached in both groups.

Only one RCT study of adults with JHS/hEDS has been performed, showing reduced knee pain and increased proprioception, in the group receiving exercises of proprioception, balance and plyometrics, compared with a matched control group receiving no exercises [Sahin et al., 2008].

A number of cohort/uncontrolled clinical studies of JHS/hEDS in children and adults report positive effects of strength, core stability and endurance training in addition to education in pain management [Bathen et al., 2013], different intensity of resistive training alone [Ferrell et al., 2004; Møller et al., 2014], and education in pain management alone [Rahman et al., 2014]; however, these reports need to be further evidenced with more rigorous research designs. Existing consensus based hospital and UK paediatric rheumatology guidelines may also offer helpful advice and treatment strategies to clinicians [The British Society for Pediatric and Adolescent Rheumatology, 2013; Cincinnati Children's Hospital Medical Center, 2014]. Qualitative interviews with 28 families with children with JHS/hEDS (5–17 years) on prerequisites for the best adherence to exercise is reported to be parental motivation adapting family routines, making exercise a family activity and seeing the benefit [Birt et al., 2014]. On the other hand are factors for non-adherence to exercise for these children, lower levels of parental supervision, not understanding the treatment, not seeing the benefit and not having specific time to dedicate for doing exercises [Birt et al., 2014].

There is some evidence for that JHS/hEDS improves with exercise, but there is no convincing evidence for specific types of exercise or that exercise is better than control [Smith et al., 2013; Palmer et al., 2014]. Both reviews recommend that longer term, rigorous high-quality multicentre RCT's are warranted for children and adults with JHS/hEDS.

Education, reassurance, manual therapy, tape, hydrotherapy, and relaxation training are used by physical therapists [Lyell et al., 2015; Palmer et al., 2015; Rombaut et al., 2011b, 2015b; Billings et al., 2015] and clinical experts recommend these strategies [Russek, 2000; Simmonds and Keer, 2007; Keer and Simmonds, 2011], based on clinical experience and some evidence of their efficacy from other patient groups. Currently there are no RCT's or comparative trials to support the efficacy of these strategies in individuals with JHS/hEDS. Therapies should be individualized [Simmonds and Keer, 2007, 2008; Simmonds et al., 2016a] and applied carefully to avoid exacerbation of pain as peripheral

and central sensitization is commonly observed [Rombaut et al., 2011b]. Although Adib et al. [2005] refer to 25% of children using mobility aids in a selected population and splints are sometimes recommended, limited effect of these aids, and splinting for hands/wrists in individuals with JHS/hEDS has been found [Smith et al., 2013].

Cardiovascular, musculoskeletal and physical fitness training parameters should be encouraged in both children and adults according to the criteria of the National Strength and Conditioning Association (NSCA) and American College of Sports Medicine (ACSM) [Faigenbaum et al., 2009; Faigenbaum and Myer, 2010; Garber et al., 2011]. In general, specialists recommend a carefully graduate exercise training prescription, underpinned by motor learning theory [Smith et al., 2014b] to avoid injury and overtraining as this may lead to loss of confidence in the physical therapist. Pain, fatigue, and fear of injury are commonly reported barriers to exercise [Simmonds et al., 2016b]. A graduated return to higher levels of sport or dance is recommended, and training loads should be observed to ensure adequate recovery.

Patients with JHS/hEDS have numerous complaints and an impaired functional status that strongly determine their high rate of treatment consumption. The outcome of surgical and physical therapy treatment is largely disappointing, which illustrates the need for a stronger evidence base [Rombaut et al., 2011a]. Education for health professionals [Billings et al., 2015; Rombaut et al., 2015b; Terry et al., 2015; Lyell et al., 2016; Russek et al., 2016] is paramount in order to optimize physical therapy provision. A recent feasibility study of a six session package of treatment demonstrates future potential [Palmer et al., 2016a,b] and further research is required to explore the specific therapeutic actions of physical therapy for managing JHS/hEDS. Recently, a meta-analysis revealed that for treatment of adults, a significant pain reduction was achieved by a variety of physical and cognitive approaches. Active modes of physical therapy are the recommended approach. However, the effectiveness on disability still needs to be established [Scheper et al., 2016c].

In cases where significant systemic signs and symptoms are observed and reported by individuals, such as cardiac dysautonomia, gastrointestinal, urinary and bladder dysfunction, referral to specialist medical teams is indicated. Readers are referred to care guidelines in these specialist areas. Physiotherapists play an important role in management through exercise prescription and patient education for many of these conditions. Relatively recent developed masterclass courses, papers, and symposia provide clinicians with information on how to adapt and apply therapies [Simmonds and Keer, 2007, 2008; Simmonds et al., 2016c].

CONCLUSION

Children, adolescents, and adults suffering from JHS/hEDS frequently present with complex symptoms and are therefore challenging for physical therapists to manage effectively. Based on the ICF, a literature overview has been presented for the assessment and management based on the best evidence available to help guiding clinicians. The current evidence-base for the physical therapy assessment and management of JHS/hEDS is limited in size and quality.

In future directions longer term, rigorous multicenter randomized controlled trials are warranted to assess the clinical and cost-effectiveness of interventions for children and adults with JHS/hEDS. There is a need for further identification and validation of suitable outcome measures. Until further multicenter trials are conducted, clinical decision-making should be theoretically applied based, underpinned by the available evidence where available. In patients diagnosed with JHS/hEDS international consensus and combined efforts to identify patient risk profiles would create a better understanding of the pathological mechanisms with the possibility of optimizing health care for affected individuals.

REFERENCES

Abonia JP, Wen T, Stucke EM, Grotjan T, Griffith MS, Kemme KA, Collins MH, Putnam PE, Franciosi JP, von Tiehl KF, Tinkle BT, Marsolo KA, Martin LJ, Ware SM, Rothenberg ME. 2013. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. J Allergy Clin Immunol 132: 378–386.

Adib N, Davies K, Grahame R, Woo P, Murray KJ. 2005. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatol 44:744–750.

Atkinson HL, Nixon-Cave K. 2011. A tool for clinical reasoning and reflection using the international classification of functioning, disability and health (ICF) framework and patient management model. Phys Ther 91:416–430.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. 2011. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64:401–406.

Bathen T, Hångmann AB, Hoff M, Andersenand L, Rand-Hendriksen S. 2013. Multidisciplinary treatment of disability in ehlers-danlos syndrome hypermobility type/hypermobility syndrome: A pilot study using a combination of physical and cognitive-behavioral therapy on 12 women. Am J Med Genet Part A 161A:3005–3011.

Beighton P, Solomon L, Soskolne CL. 1973. Articular mobility in an African population. Ann Rheumatic Dis 32:413–418.

Beighton P, De Paepe A, Steinmann B, Tsipourasand P, Wenstrup RJ. 1998. Ehlers-Danlos syndromes: Revised nosology, villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet 77:31–37.

Billings S, Deane JA, Bartholomew J, Simmonds JV. 2015. Knowledge and perceptions of joint hypermobility syndrome amongst pediatric physiotherapists. J Physiother Pract Res 36:33–51.

Birt L, Pfeil M, MacGregor A, Armon K, Poland F. 2014. Adherence to home physiotherapy treatment in children and young people with joint hypermobility: A qualitative report of family perspectives on acceptability and efficacy. Musculoskel Care 12:56–61.

Carbone L, Tylavsky FA, Bush AJ, Koo W, Orwoll E, Cheng S. 2000. Bone density in Ehlers-Danlos syndrome. Osteoporos Int 11:388–392.

Cederlöf M, Larsson H, Lichtenstein P, Almqvist C, Serlachius E, Ludvigsson JF. 2016. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. BMC Psychiatry 16:207.

Clark C, Khattab A, Carr E. 2014. Chronic widespread pain and neurophysiological symptoms in Joint Hypermobility Syndrome. Int J Ther Rehab 21:60–68.

Clarke C, Simmonds JV. 2011. An exploration of the prevalence of hypermobility syndrome in Omani women attending an outpatient department. Musculoskel Care 9:1–10.

Connelly E, Hakim A, Davenport HS, Simmonds JV. 2015. A Study exploring the prevalence of Hypermobility Syndrome in a musculoskeletal triage clinic. Physiother Res Pract 36:43–53.

de Kort LM, Verhulst JA, Engelbert RH, Uiterwaal CS, de Jong TP. 2003. Lower urinary tract dysfunction in children with generalized hypermobility of joints. J Urol 170:1971–1974.

De Paepe A, Malfait F. 2012. The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genet 82:1–11.

De Wandele I, Rombaut L, Leybaert L, Van de Borne P, De Backer T, Malfait F, De Paepe A, Calders P. 2014. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers—Danlos syndrome. Semin Arthritis Rheum 44:93–100.

El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. 2005. Lower limb pain in a preadolescent population: Prognosis and risk factors for chronicity—A prospective 1- and 4-year follow-up study. Pediatrics 116:673–681.

Engelbert RH, Bank RA, Sakkers RJ, Helders PJ, Beemer FA, Uiterwaal CS. 2003. Pediatric generalized joint hypermobility with and without musculoskeletal complaints: A localized or systemic disorder? Pediatrics 111: e248–e254.

Engelbert RH, van Bergen M, Henneken T, Helders PJ, Takken T. 2006. Exercise tolerance in children and adolescents with musculoskeletal pain in joint hypermobility and joint hypomobility syndrome. Pediatrics 118:e690–e696.

Evans AM, Rome K. 2011. A Cochrane review of the evidence for non-surgical interventions for flexible pediatric flat feet. Eur J Phys Rehabil Med 47:69–89.

Evidence based Care Guideline for Management of Pediatric Joint Hypermobility Guideline Copyright © 2014. Cincinnati Children's Hospital Medical Center, James M. Anderson Center for Health Systems Excellence Evidence Based Care Guideline Identification and management of Pediatric Joint Hypermobility In children and adolescents aged 4 to 21 years old Publication Date: October 21, 2014.

Faigenbaum AD, Kraemer WJ, Blimkie CJ, Jeffreys I, Micheli LJ, Nitka M, Rowland TW. 2009. Youth resistance training: Updated position statement paper from the national strength and conditioning association. J Strength Cond Res 23:S60–S79.

Faigenbaum AD, Myer GD. 2010. Resistance training among young athletes: Safety, efficacy and injury prevention effects. Br J Sports Med 44:56–63.

Falkerslev S, Baagø C, Alkjær T, Remvig L, Halkjær-Kristensen J, Larsen PK, Juul-Kristensen B, Simonsen EB. 2013. Dynamic balance during gait in children and adults with Generalized Joint Hypermobility. Clin Biomech (Bristol Avon) 28:318–324.

Fatoye F, Palmer S, Macmillan F, Rowe PP, van der Linden M. 2009. Proprioception and muscle torque deficits in children with hypermobility syndrome. Rheumatol 48:52–57.

Fatoye FA, Palmer S, van der Linden ML, Rowe PJ, Macmillan F. 2011. Gait kinematics and passive knee joint range of motion in children with hypermobility syndrome. Gait Post 33:447–451.

Ferrell WR, Tennant N, Baxendale RH, Kusel M, Sturrock RD. 2007. Musculoskeletal reflex function in the joint hypermobility syndrome. Arthr Care and Res 57:1329–1333.

Ferrell WR, Tennant N, Sturrock RD. 2004. Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthr Rheum 50:3323–3328.

Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP. 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med Sci Sports Exerc 43:1334–1359.

Grahame R, Hakim AJ. 2008. Hypermobility. Curr Opin Rheumatol 20:106–110.

Grahame R, Bird HA, Child A. 2000. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol 27:1777–1779.

Guidelines for Management of Joint Hypermobility Syndrome in Children and Young People. 2013. The British Society for Pediatric and Adolescent Rheumatology. Available online https://www.google.co.uk/?gws_rd=ssl#q=bspar+for+hypermobility. Publication Date: 20. 6.2013.

Hanewinkel-van Kleef YB, Helders PJ, Takken T, Engelbert RH. 2009. Motor performance in children with generalized hypermobility: The influence of muscle strength and exercise capacity. Pediatr Phys Ther 21:194–200.

Jansson A, Saartok T, Werner S, Renstrom P. 2004. General joint laxity in 1845 Swedish school children of different ages: Age- and gender-specific distributions. Acta Pardiatr 93:1202–1206.

Juul-Kristensen B, Schmedling K, Rombaut L, Lund H, Engelbert RH. 2017. Measurement properties of clinical assessment methods for diagnosing generalised joint hypermobility—A systematic review. Am J Med Genet part C submitted, in press.

Keer R, Simmonds JV. 2011. Joint protection and physical rehabilitation of the adult with hypermobility syndrome. Cur Opinions Rheumatol 23:131–136.

Kemp S, Roberts I, Gamble C, Wilkinson S, Davidson JE, Baildam EM, Cleary AG, McCann LJ, Beresford MW. 2010. A randomized comparative trial of generalized vs targeted physiotherapy in the management of childhood hypermobility. Rheumatol (Oxford) 49:315–325.

Kirby A, Davies R. 2007. Developmental coordination disorder and joint hypermobility syndrome—Overlapping disorders? implications for research and clinical practice. Child Care Health Dev 33:513–519.

Kirby A, Davies R, Bryant A. 2005. Hypermobility syndrome and developmental coordination disorder: Similarities and features. Int J Ther Rehabil 12:431–443.

Lyell M, Simmonds JV, Deane J. 2015. Physiotherapists' knowledge and management of adults with hypermobility and joint hypermobility syndrome in the UK; A nationwide survey. Poster, WCPT May, Singapore. Physiotherapy 101:e919.

Lyell M, Simmonds JV, Deane JA. 2016. Future of education in hypermobility and hypermobility syndrome. J Physiother Pract and Res 37:101–109.

Mastoroudes H, Giarenis I, Cardozo L, Srikrishna S, Vella M, Robinson D, Kazkazand H, Grahame R. 2013. Lower urinary tract symptoms in women with benign joint hypermobility syndrome: A case-control study. Int Urogynecol J 24:1553–1558.

Mintz-Itkin R, Lerman-Sagie T, Zuk L, Itkin-Webman T, Davidovitch M. 2009. Does physical therapy improve outcome in infants with joint hypermobility and benign hypotonia? J Child Neurol 24:714–719.

Morrison SC, Ferrari J, Smillie S. 2013. Assessment of gait characteristics and orthotic management in children with Developmental Coordination Disorder: Preliminary findings to inform multidisciplinary care. Res Dev Disabil 34:3197–3201.

Møller MB, Kjær M, Svensson RB, Andersen JL, Magnusson SP, Nielsen RH. 2014. Functional adaptation of tendon and skeletal muscle to resistance training in three patients with genetically verified classic Ehlers Danlos Syndrome. Muscles Ligaments Tendons J 4:315–323.

Murray KJ. 2006. Hypermobility disorders in children and adolescents. Best Pract Res Clin Rheumatol 20:329–351.

Nijs J, Van Essche E, De Munck M, Dequeker J. 2000. Ultrasonographic, axial, and peripheral measurements in female patients with benign hypermobility syndrome. Calcif Tissue Int 67:37–40.

Pacey V, Nicholson L, Adams R, Munn J, Munns C. 2010. Generalised joint hypermobility and injury risk of lower limb injury during sport. Am J Sports Med 38:1487–1497.

Pacey V. 2014. PhD thesis: Joint Hypermobility Syndrome in Children, University of Sydney, Sydney, Australia.

Pacey V, Adams RD, Tofts L, Munns CF, Nicholson LL. 2015a. Joint hypermobility syndrome subclassification in paediatrics: A factor analytic approach. Arch Dis Child 100:8–13.

Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. 2015b. Quality of life prediction in children with joint hypermobility syndrome. J Paediatr Child Health 51:689–695.

Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. 2013. Exercise in children with joint hypermobility syndrome and knee pain: A randomised controlled trial comparing exercise into hypermobile versus neutral knee extension. Pediatr Rheumatol Online J11:30.

Palmer S, Bailey S, Barker L, Barney L, Elliott A. 2014. The effectiveness of therapeutic exercise for joint hypermobility syndrome: A systematic review. Physiotherapy 100:220–227.

Palmer S, Cramp F, Lewis R, Shahid M, Clark E. 2015. Diagnosis, management and assessment of adults with joint hypermobility syndrome: A UK-Wide survey of physiotherapy practice. Musculoskeletal Care 13:101–111.

Palmer S, Terry R, Rimes KA, Clark C, Simmonds J, Horwood J. 2016a.

Physiotherapy management of joint hypermobility syndrome—A focus group study of patient and health professional perspectives. Physiother 102:93–102.

Palmer S, Cramp F, Clark E, Lewis R, Brookes S, Hollingworth W, Welton N, Thom N, Terry R, Rimes KA, Horwood J. 2016b. The feasibility of a randomised controlled trial of physiotherapy for adults with joint hypermobility syndrome. Health Technol Assess 20:1–264.

Rahman A, Daniel C, Grahame R. 2014. Efficacy of an out-patient pain management programme for people with joint hypermobility syndrome. Clin Rheumatol 33:1665–1669.

Remvig L, Jensen DV, Ward C. 2007. Are diagnostic criteria for general joint hypermobility andbenign joint hypermobility syndrome based on reproducible and valid tests? A review of the literature. J Rheumatol 34:798–803.

Remvig L, Engelbert RH, Berglund B, Bulbena A, Byers PH, Grahame R, Juul-Kristensen B, Lindgren KA, Uitto J, Wekre LL. 2011. Need for a consensus on the methods by which to measure joint mobility and the definition of norms for hypermobility that reflect age, gender and ethnic-dependent variation: Is revision of criteria for joint hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type indicated? Rheumatol 50:1169–1171.

Rombaut L, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert RH, Calders P. 2015a. Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: Evidence for generalized hyperalgesia. Clin Rheumatol 34:1121–1129.

Rombaut L, Deane J, Simmonds J, De Wandele I, De Paepe A, Malfait F, Calders P. 2015b. Knowledge, assessment, and management of adults with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type among Flemish physiotherapists. Am J Med Genet C Semin Med Genet 169C:76–83.

Rombaut L, Malfait F, De Wandele I, Taes Y, Thijs Y, De Paepe A, Calders P. 2012. Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken) 64:1584–1592.

Rombaut L, Malfait F, De Wandele I, Thijs Y, Palmans T, De Paepe A, Calders P. 2011a. Balance, gait, falls, and fear of falling in women with the hypermobility type of Ehlers-Danlos syndrome. Arthr Care Res (Hoboken) 63:1432–1439.

Rombaut L, Malfait F, De Wandele I, Cools A, Thijs Y, De Paepe A, Calders P. 2011b. Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. Arch Phys Med Rehabil 92:1106–1112.

Russek L. 2000. Examination and treatment of a patient with hypermobility syndrome. Phys Ther 80:386–398.

Russek LN, LaShomb EA, Ware AM, Wesner SM, Westcott V. 2016. United States physical therapists' knowledge about joint hypermobility syndrome compared with fibromyalgia and rheumatoid arthritis. Physiother Res Int 21:22–35.

Sahin N, Baskent A, Cakmak A, Salli A, Ugurlu H, Berker E. 2008. Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. Rheumatol Int 28:995–1000.

Scheper MC, Engelbert RH, Rameckers EA, Verbunt J, Remvig L, Juul-Kristensen B. 2013. Children with generalised joint hypermobility and musculoskeletal complaints: State of the art on diagnostics, clinical characteristics, and treatment. Biomed Res Int 2013:121054.

Scheper MC, de Vries JE, Verbunt J, Engelbert RH. 2015. Chronic pain in hypermobility syndrome and Ehlers—Danlos syndrome (hypermobility type): It is a challenge. J Pain Res 20:591–601.

Scheper MC, Juul-Kristensen B, Rombaut L, Rameckers EA, Verbunt J, Engelbert RH. 2016a. Disability in adolescents and adults diagnosed with hypermobility related disorders: A meta-analysis. Arch Phys Med Rehabil 97:2174–2187.

Scheper MC, Pacey V, Rombaut L, Adams RD, Tofts L, Calders P, Nicholson LL, Engelbert RH. 2016b. Generalized Hyperalgesia in children and adults diagnosed with Hypermobility Syndrome and Ehlers-Danlos Hypermobility type: A discriminative analysis. Arthr Care Res 15:1–7.

Scheper MC, Rombaut LL, de Vries JE, de Wandele I, Esch van M, Calders P, Engelbert RH. 2016c. Factors of activity impairment in adult patients with Ehlers Danlos Syndrome hypermobility type): Muscle strength and proprioception. Disabil Rehabil 24:1–7.

Simmonds JV, Keer RJ. 2007. Hypermobility and the hypermobility syndrome. Masterclass Man Ther 12:298–309.

Simmonds JV, Keer RJ. 2008. Hypermobility and the hypermobility syndrome. Masterclass. Illustrated via case studies, part II. Man Ther 13:e1–e11.

Simmonds J, Herbland A, Hakim A, Ninis N, Lever W, Aziz Q, Cairns M. 2016a. Attitudes, beliefs and behaviours towards exercise amongst individuals with joint hypermobility syndrome/Ehlers Danlos syndrome—hypermobility type IFOMPT Proceedings. Man Ther 25:335336.

Simmonds JV, Pacey V, Keer RJ, Castori MM. 2016b. Advancing practice in hypermobility Syndrome/Ehlers Danlos syndrome—hypermobility type focused symposium. IFOMPT, glasgow, UK. Man Ther 25: e21–e22.

Simmonds JV, Herbland A, Hakim A, Ninis N, Lever W, Aziz Q, Cairns M. 2016c. Attitudes, beliefs and behaviours towards exercise amongst individuals with joint hypermobility syndrome/Ehlers Danlos syndrome—hypermobility type IFOMPT, Glasgow, UK. Man Ther 25:e35–e36.

Smith TO, Jerman E, Easton V, Bacon H, Armon K, Poland F, Macgregor AJ. 2013. Do people with benign joint hypermobility syndrome (BJHS) have reduced joint proprioception? A systematic review and meta-analysis. Rheumatol Int 33:2709–2716.

Smith TO, Easton V, Bacon H, Jerman E, Armon K, Poland F, Macgregor AJ. 2014a. The relationship between benign joint hypermobility syndrome and psychological distress: A systematic review and meta-analysis. Rheumatol (Oxford) 53:114–122.

Smith TO, Bacon H, Jerman E, Easton V, Armon K, Poland F, Macgregor AJ. 2014b. Physiotherapy and occupational therapy interventions for people with benign joint hypermobility syndrome: A systematic review of clinical trials. Disabil Rehabil 36:797–803.

Terry RH, Palmer ST, Rimes KA, Clark CJ, Simmonds JV, Horwood JP. 2015. Living with joint hypermobility syndrome: Patient experiences of diagnosis, referral and self-care. Fam Pract 32:354–358.

Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D. 2009. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet Part A 149A:2368–2370.

Voermans NC, Knoop H. 2011. Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 33:706–707.

World Health Organization. 2015. International Classification for Functioning Disability and Health. http://www.who.int/classifications/icf/en/ [Accessed April 2016].

Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, Aziz Q. 2010. Unexplained gastrointestinal symptoms and joint hypermobility: Is connective tissue the missing link? Neurogastroenterol Motil 22:252–278.