



Difficulties in diagnosis and selection of optimal diagnostic methods for hypermobile Ehlers Danlos Syndrome – literature review

Trudności w diagnozowaniu i wybór optymalnych metod diagnostycznych hipermobilnego zespołu Ehlersa-Danlosa: przegląd piśmiennictwa

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Abstract

Introduction and objective. Ehlers Danlos Syndrome – Hypermobile Type (EDS-HT), in which the genetic basis could not be determined and mutations of collagen fibrillar proteins were excluded, is one of the most common types of EDS. It is a disease characterized by many symptoms of varying severity. The purpose of the study is to determine the most important diagnostic factors for EDS-HT based on current literature.

Materials and method. Searching PubMed publication databases, Google Scholar and Science Direct, by using a combination of key words: hEDS *diagnosis, hypermobile EDS, hypermobility.*

Brief description of the state of knowledge. 19 papers were selected for the literature review, among which 8 concern the adequacy of the Beighton result in the diagnosis of EDS-HT, and another 11 the quality of life of people with EDS-HT, as well as the assessment and diagnosis of other symptoms accompanying this disease.

Conclusions. In order to diagnose EDS-HT, one should be guided not only by the established standard, which is the Beighton score, but also by additional tests that would confirm the diagnostic decision and reduce the risk of error. Extension of diagnostic tests with additional criteria, which are presented in the article, would make diagnoses more accurate and reduce the possibility of false diagnoses. This is very important from the perspective of implementing appropriate treatment and the mental comfort of the patient.

Key words

Ehlers-Danlos Syndrome, EDS-HT diagnosis, hypermobility type, hEDS

Streszczenie

Wstęp i cel pracy. Hipermobilny zespół Ehlersa-Danlosa (Ehlers-Danlos syndrome – hypermobile type, EDS-HT), którego podłoża genetycznego nie udało się ustalić, przy czym wykluczono mutacje białek fibrylarnych kolagenu, jest jednym z najczęściej występujących typów EDS. Jest to schorzenie cechujące się wieloma objawami o różnym nasileniu. Celem publikacji jest ustalenie najważniejszych czynników diagnostycznych EDS-HT na podstawie aktualnego piśmiennictwa.

Materiały i metody. Przeszukanie baz publikacji Pubmed, Google Scholar oraz Science Direct, poprzez użycie kombinacji słów kluczy: hEDS *diagnosis, hypermobile EDS, hypermobility.*

Aktualny stan wiedzy. Ostatecznie do przeglądu literatury włączono 19 prac, wśród których 8 dotyczy adekwatności wyniku Beightona w diagnostyce EDS-HT, a kolejne 11 jakości życia osób z EDS-HT oraz oceny i diagnostyki innych objawów towarzyszących temu schorzeniu.

Podsumowanie. W celu diagnozy EDS-HT należy kierować się nie tylko ustalonym standardem, jakim jest wynik Beightona, ale także dodatkowymi testami, które potwierdziłyby decyzję diagnostyczną i zmniejszyły ryzyko błędu. Rozszerzenie badań diagnostycznych o dodatkowe kryteria, m.in. przedstawione w autorskim artykule, pozwoliłoby na zmniejszenie liczby fałszywych diagnoz oraz trafniejsze ich stawianie. Jest to bardzo ważne z perspektywy wdrożenia odpowiedniego leczenia i komfortu psychicznego pacjenta.

Słowa kluczowe

zespół Ehlersa-Danlosa, diagnoza EDS-HT, typ hipermobilny, hEDS

INTRODUCTION

Ehlers Danlos Syndrome (EDS) is a broad group of genetic, hereditary connective tissue disorders[1]. Depending on the type of EDS, the disease can be inherited autosomally dominant, recessive, or *de novo* [2–4]. Currently, due to the wide spectrum of symptoms and their different severity, 13

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types of EDS have been distinguished. However, the most frequent types of EDS are: classic, hypermobile, vascular, kyphoscoliotic and arthrochalasia [5, 6]. This division is based on clinical disease manifestations and genetic causes in each of EDS [7].

It is estimated that EDS occurs, on average, in 1/5,000 births in the world population, where the hypermobile type is most common and 90% are women [8, 9]. Among the basic symptoms of EDS are elastic skin, susceptibility to injuries and hypermobility of joints [1,10]. The skin of people with EDS in most types is very delicate and thin giving the impression of being translucent [1–3, 10–16]. Wounds take a long time to heal, and in the case of 4 other types of EDS not previously mentioned, the damage leaves atrophic scars [15]. Attention should be paid to hypermobility of the joints, which, despite being a characteristic symptom, especially of the hypermobile type, makes it difficult to distinguish EDS from Marfan Syndrome or Loeys-Dietz. The hypermobile type is the most common type of EDS [17]. Correct and early diagnosis is crucial because joint dislocations may appear at birth and gradually progress, causing problems with standing and sitting as a result of muscular hypotension [18]. In addition, it has been observed that one of the first symptoms may be frequently repeated dislocations of the temporomandibular joints during eating or yawning due to overstretched ligaments [19].

Due to the development of molecular diagnostic tests, more than 19 mutations responsible for the formation of particular types of the disease have been identified, mainly in the process of post-translational processing of fibrillar collagen proteins or their enzymes [2, 18]. The exception is hypermobile EDS (EDS-HT), wherein the genetic background and mutations in collagen fibrillar proteins were excluded [2]. The results of the genetic tests carried out so far have not been able to establish a universal marker; however, a group in which the decrease or absence of the tenascin-X gene was observed has been identified [2, 20]. Tenascin-X is a glycoprotein expressed in the skin, joints and muscles [21]. With its deficiency, collagen density decreases and fibrils are fragmented [22]. Tenascin-X has not yet been recognized as a universal biomarker for EDS-HT, and changes in its gene are more often attributed to the rarer type, classic-like EDS [14].

Currently, EDS diagnosis is based on medical history and confirmed by genetic tests or skin biopsy [23]. Because EDS-HT does not have a universal biomarker, an interview and physical examination are used based on Beighton's criterion and score, which determines the degree of joint hypermobility. Excessive joint mobility is found when two main criteria, one main criterion and two smaller or four smaller criteria are met. The main criteria are the Beighton score, which is equal to or higher than 5/9 and joint pain in four or more joints for more than three months. Smaller criteria include joint or back pain lasting more than three months, repetitive dislocations, soft tissue rheumatism, thin and stretchy skin, marfanoid body appearance, or Beighton score above one [7, 24]. The test that makes up the Beighton score is the assessment of the stretchability of nine joints: knee, elbow, phalange and spine, where one point is given to each joint presenting excessive mobility [25]. However, it is observed that 30% of the population is able to obtain a clinically significant result in this test, and 40% of women fulfil the Beighton's criteria [17]. A family history is also not a sufficient inclusion criterion if only the occurrence of

hypermobility is taken into account, and cannot guarantee the absence of false positive results [17].

EDS is a disease characterized by many symptoms of varying severity. Diagnosis is also hampered by the lack of an effective genetic test. The purpose of this study is to determine the most important EDS-HT diagnostic factors based on current literature.

MATERIALS AND METHOD

In order to carry out the review, relevant literature was found using Pubmed, Google Scholar and Science Direct publication databases, using a combination of key words: *hEDS diagnosis, hypermobile EDS, hypermobility*. Nineteen articles were selected on this basis from the last five years (2014–2019) that contained the above-mentioned key words (Tab. 1). Exclusion criteria were: papers older than five years, conference materials and articles written in a language other than Polish or English, or with a study group of less than five people (Tab.1).

Description of the state of knowledge. Selected publications present various types of tests highlighting the complexity of EDS-HT by examining the symptoms, or effects of the disease other than only a hypermobility of the joints (Tab. 2). The difficulty in diagnosing EDS-HT lies in the insufficient specificity of the Beighton score and family history. As can be seen in the above works, diagnostics was extended by additional parameters or accompanying symptoms in order to complete the profile of the disease and its better understanding.

A repeated test in the works of Skwiot et al. [26], Schlager et al. [27], Birch et al. [28] and De Wandele et al. [29], is the Beighton score, which determines the mobility of specific joint, however, each of these groups used additional tests to confirm the diagnosis. The publication by Skwiot et al. [26] used the Grahame and Hakim questionnaire and the Sachse criteria. The research of Schlager et al. [27] was based on three methods Which, in addition to Beighton's score, used Contompasi's score and Hospital del Maria criteria. Birch et al. [28] complemented their research with the Short Form-36 (SF-36) questionnaire.

De Wandele et al. [29] studying the phenomenon of dysautonomy among patients with EDS-H, took into account the cardiological assessment of the function of the autonomic system (including Autonomic Reflex Screen, ARS), deep breathing, orthostatic hypotension and middle ear condition. Similar studies were conducted by the Celletti [30] group, which examined the involvement of the cardiovascular system in EDS-HT using the Valsalva manoeuvre deep breathing and orthostatic hypotension [30]. The study was additionally expanded to include variability in heart rate and blood pressure. David Cypel in his work took into account the degree of shoulder joint deviation as a factor indicating hypermobility of joints [31].

Two other research groups noted the symptoms associated with EDS-HT, such as intestinal disorders and obstructive sleep apnea. Menys et al. [32] used magnetic resonance imaging for this purpose. Gaisl et al. [33] used level-3 respiratory polygraphy. In both studies, EDS-HT patients were qualified based on Beighton's score.

Many other people checked the effectiveness of other diagnostic tests against Beighton's result. Whitehead et al.

Table 1. Publications used in the review (*title, aim, materials and methods*)

Authors, Year of publication	Title, aim, materials and methods
Skwiot et al., 2019 [26]	Title: Hypermobility of Joints in Dancers Aim: to study the prevalence of Joint Hypermobility Syndrome (JHS) by analyzing its presence in accordance with numerous diagnostic criteria. Materials and Method: 77 dancers were interviewed, Beighton's score, Grahame and Hakim's questionnaire and Sachs's criterion were used.
Schlager et al., 2018 [27]	Title: Inter- and Intra-Rater Reliability for Measurement of Range of Motion in Joints Included in Three Hypermobility Assessment Methods Aim: to examine the inter- and intra-rate reliability for joint motion measurements using three methods of hypermobility assessment and a structured protocol. Materials and methods: Healthy adults: 49 for inter- and 29 for intra-rater assessments using the Beighton and Contompasisscore and the Hospital del Mar criteria.
Birch et al., 2015 [28]	Title: No Correlations Between Radiological Angles and Self-Assessed Quality of Life in Patients With Hip Dysplasia at 2-13 Years of Follow-Up After Periacetabular Osteotomy Aim: to investigate the quality of life associated with the health of patients with hip dysplasia after periacetabular osteotomy and to determine whether quality of life is associated with acetabular angles or excessive joint mobility. Materials and methods: 228 patients completed the SF-36 questionnaire and Beighton's result, which were later compared with a Danish population; the angles of the middle edge and the acetabular index were measured before and after the periacetabular osteotomy, and the relationship to the quality of life of the patients was examined by logistic regression.
De Wandele et al., 2014 [29]	Title: Dysautonomia and Its Underlying Mechanisms in the Hypermobility Type of Ehlers-Danlos Syndrome Aim: to investigate whether dysautonomia is present in EDS-HT and to discover the underlying mechanisms. Materials and Method: 39 women with EDS-HT and 35 healthy women from the control group underwent tests of autonomic functions, such as heart rate variability and baroreflex sensitivity analysis, Autonomic Reflex Screen, measurement of skin stretch, Beighton's score and questionnaires.
Celletti et al., 2017 [30]	Title: Orthostatic Intolerance and Postural Orthostatic Tachycardia Syndrome in Joint Hypermobility Syndrome / Ehlers-Danlos Syndrome, Hypermobility Type: Neurovegetative Dysregulation or Autonomic Failure? Aim: to further evaluate the autonomic involvement of the cardiovascular system in JHS / EDS-HT using a set of functional tests. Materials and Method: 35 JHS / EDS-HT patients checked for responses to cardiovascular reflex tests, including deep breathing, Valsalva manoeuvre, orthostatic hypotension test, heart rate and blood pressure variability, using spectral analysis compared to age matched group and gender.
Cypel, 2018 [31]	Title: Gleno-humeral abduction measurement in patients with Ehlers-Danlos syndrome Aim: to test the hypothesis whether shoulder joint deviation measurement by a validated method helps to diagnose EDS-HT. Materials and Method: a case-control retrospective study involving 110 people, diagnosed with EDS-HT and a control group of 100 people.
Menys et al., 2017 [32]	Title: A Magnetic Resonance Imaging Study of Gastric Motor Function in Patients With Dyspepsia Associated With Ehlers-Danlos Syndrome-Hypermobility Type: A Feasibility Study Aim: to examine the feasibility of a protocol lasting less than 60 minutes using a water test to assess gastric emptying, motility and accommodation in a group of EDS-HT patients with dyspepsia. Materials and Method: nine women with an average age of 33 years were examined for gastric emptying time, motility and accommodation, which were calculated based on the observation of two independent observers for each EDS-HT patient, and compared with matched control using paired statistics.
Gaisl et al., 2017 [33]	Title: Obstructive Sleep Apnoea and Quality of Life in Ehlers-Danlos Syndrome: A Parallel Cohort Study Aim: to investigate the prevalence of obstructive sleep apnea as a cause of fatigue, excessive daytime sleepiness and reduced quality of life in the EDS-HT population. Materials and Method: a prospective study with parallel groups of 100 participants in total, where 46 with diagnosed EDS-HT were compared with a control group of 100 healthy adults; the groups underwent structured interviews and a level-3 respiratory polygraphy
Whitehead et al., 2018 [34]	Title: Does the Beighton Score Correlate With Specific Measures of Shoulder Joint Laxity? Aim: to assess the correlation between Beighton's score and validated measurements of shoulder relaxation. Materials and Method: 160 subjects were examined for shoulder joint external rotation, abduction and stability, after which the correlation of the results obtained with the Beighton's score was examined.
Nicholson et al., 2018 [35]	Title: The Upper Limb Hypermobility Assessment Tool: A novel validated measure of adult joint mobility Aim: to assess the reliability of measuring the mobility of the upper limb joint and use it to classify hypermobility. Materials and Method: 112 subjects were divided into 3 groups: healthy, hypermobility and undiagnosed who were suspected of having a disease. Each group was subjected to the Upper Limb Hypermobility Assessment Tool (ULHAT) test, Beightonscore and clinical opinion.
Johnson et al., 2019 [36]	Title: The Lower Limb Assessment Score: A valid measure of hypermobility in elite football? Objective: validation of the Lower Limb Assessment Score (LLAS) on a group of players for future studies determining the effect of hypermobility of the lower limbs on the risk of injury. Materials and Method: 36 professional players passed LLAS and Beighton's score, which were then compared.
Nourissat et al., 2018 [37]	Title: Diagnosis of Ehlers-Danlos syndrome after a first shoulder dislocation Aim: to determine if clinical symptoms may signal the presence of EDS-HT at the first shoulder dislocation. Materials and Method: clinical and radiological data were collected from 27 patients with unstable shoulder, and a 40-person control group with surgery on the unstable shoulder. All injuries, disorders and family history, as well as radiological data were included in the assessment.
Romeo et al., 2016 [38]	Title: Assessing Joint Hypermobility in Preschool-Aged Children Aim: to investigate the usefulness and reliability of the Beighton score in children under 5 years of age with genetic disorders associated with hypermobility. Materials and Method: 284 healthy children and 26 children with preschool genetic disorders (younger than 5 years) were tested for Beighton's score.
Palmer et al., 2017 [39]	Title: Test-retest reliability and smallest detectable change of the Bristol Impact of Hypermobility (BioH) questionnaire. Aim: to determine the credibility of the Bristol Impact of Hypermobility questionnaire compared to the Short Form-36 result. Materials and Method: 233 patients completed the questionnaires twice with an interval of 2 weeks. Test analyses were performed on stable patients.
Manns et al., 2018 [40]	Title: A qualitative evaluation of the appropriateness, validity, acceptability, feasibility and interpretability of the Bristol Impact of Hypermobility (BioH) questionnaire Aim: to assess the adequacy, validity, acceptability, feasibility and interpretability of the Bristol Impact of Hypermobility (BioH) test. Materials and Method: 11 adults with known hypermobility of the joints, and 9 physiotherapists expressed their opinion about the tests through cognitive telephone interviews.
Armstrong et al., 2018 [41]	Title: The Beighton score as a predictor of Brighton criteria in sport and dance Aim: The effectiveness of the Beighton score as a predictor of Brighton criteria components depending on gender and sports participation. Materials and Method: 65 females and 38 males rugby players, 42 female dancers and 61 netball players were examined according to the Beighton score, and then assessed by the Brighton criteria to diagnose them with joint hypermobility syndrome.

Table 1. Publications used in the review (*title, aim, materials and methods*) (*continuation*)

Authors, Year of publication	Title, aim, materials and methods
Bevilacqua Junior et al., 2015 [42]	Title: Measuring joint hypermobility using the hospital del mar criteria—a reliability analysis using secondary data analysis Aim: detailed reliability assessment of the Hospital Del Mar criteria. Materials and Method: Secondary analysis of data from a retrospective study on a cohort of children under the age of 16 years, presenting to a joint assessment clinic and examined by the Hospital Del Mar criteria.
Berglund et al., 2015 [43]	Title: Self-reported quality of life, anxiety and depression in individuals with Ehlers-Danlos syndrome (EDS): A questionnaire study Aim: establishment of the level of anxiety and quality of life in a group of Swedish individuals with Ehlers Danlos Syndrome Materials and Method: 365 members over 18 years of the Swedish National EDS Association and 250 with EDS diagnosis participated in a postal survey containing the Hospital Anxiety and Depression Scale (HADS) and SF-36 questionnaires.
De Wandele et al., 2014 [44]	Title: Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: A comparative study with two other EDS types, fibromyalgia, and healthy controls Aim: insight into the profile and importance of autonomic symptoms in the hypermobility type of Ehlers-Danlos syndrome Materials and Method: 80 people diagnosed with EDS-HT, 18 with 2 other types of EDS and 43 as a control group assessed for the autonomic symptom profile (ASP), and filled in questionnaire about quality of life (QOL, SF-16), hypermobility (GHQ), fatigue (CIS), pain (PDQ), affective distress (HADS), and physical activity (Baecke).

Table 2. Results of publications used in the review.

Authors	Results
Skwiot et al. [26]	The frequency of hypermobility varied significantly, depending on the adopted criteria ($p = 0.001$) with the Beighton result, Grahame and Hakim questionnaire and Sachse criteria identifying 64.9%, 74% and 59.7% of patients, respectively. Hypermobility was significantly more common in women than in men ($p < 0.05$).
Schlager et al. [27]	The difference between the scores was within 5 degrees in all but one joint. The standard measurement error was 1.0 - 6.9 degrees. Reliability of the assessment of the group and unit of the frequency of positive hypermobility showed that Cohen's κ for total results was 0.54-0.78 and 0.27-0.78, respectively, and for single joints 0.21-1.00 and 0, respectively, 19-1,00.
Birch et al. [28]	For both men and women, the result of the SF-36 questionnaire after surgery was significantly lower than for reference data for the Danish population, especially in terms of physical health. No relationship was found between the central edge angles and the acetabular index of patients before or after periacetabularostectomy, and their quality of life.
De Wandele et al. [29]	The EDS-HT group showed autonomic dysregulation with increased sympathetic activity at rest and reduced sympathetic reactivity to stimuli. Orthostatic intolerance occurred much more frequently in EDS-HT than in the control group (74% vs 34%), and was most often expressed as orthostatic tachycardia in the orthostatic position. Lower QSART responses suggest that sympathetic neurogenic disorders are common in patients ($p < 0.013$), which may explain dysautonomy in EDS-HT.
Celletti et al. [30]	37.2% of the respondents were unable to complete the test. When leaning, 48.6% of patients showed orthostatic tachycardia in orthostatic position, 31.4% orthostatic intolerance, 20% normal results. Only one patient had orthostatic hypotension. Spectral analysis showed significantly higher values of baroreflex sensitivity at rest compared to controls
Cypel [31]	Shoulder deviations were significantly greater in the study group compared to the control group, regardless of age, gender and Beighton's score. The joint deviation test by more than 90° was 92.5% sensitive and 96.4% specific; the tests confirmed its repeatability.
Menys et al. [32]	The median gastric emptying time did not differ significantly from the control group, mobility after challenge with water was lower in patients with EDS-HT (11%), compared to the control (22%). Gastrointestinal accommodation in the EDS-HT group with dyspepsia was slightly reduced relative to the control group.
Gaisl et al. [33]	The severity of obstructive sleep apnea was associated with daytime sleepiness and lower quality of life in the EDS group. There was no evidence of a difference between the 2 groups studied in terms of craniofacial phenotypes.
Whitehead et al. [34]	A positive Beighton result was a poor predictor of abnormal shoulder relaxation, with low sensitivity (range 0.40-0.48) and low positive predictive values (range 0.13-0.31)
Nicholson et al. [35]	The ULHAT test distinguished each of the 3 groups and identified general hypermobility. The cut-off point was set above or equal to 7 out of 12 points.
Johnson et al. [36]	A significant correlation was found between LLAS and Beighton's score. The new test has a sensitivity of 67% and a specificity of 94%, with a cut-off point equal to or greater than 4 out of 12 points.
Nourissat et al. [37]	Significant shoulder hypermobility associated with EDS-HT was detected in a group of females under 14 years of age. Pain-free joint dislocation was also noticed, with pain after its dislocation. However, no difference in joint flexibility was noted.
Romeo et al. [38]	A Beighton score less than or equal to 4 was shown by over 90% of healthy children, and a score greater than 4 was obtained by 7% of healthy children and 89% of children with genetic disorders.
Palmer et al. [39]	In total, 462 responses were received that showed greater BloH test reliability and less for SF-36
Manns et al. [40]	Both patients and physiotherapists positively assessed BloH. The questionnaire was considered comprehensive, with a very limited number of potential missing areas related to the use of hands.
Armstrong et al., [41]	The Beighton score is an effective predictor of joint arthralgia, dislocation and subluxation.
Bevilacqua Junior et al., [42]	52.3% of boys and 47.6% of girls were diagnosed with joint hypermobility, which makes the Hospital Del Mar criteria a reliable tool. Although, specific thresholds depending on age and ethnicity should be established.
Berglund et al., [43]	74.8% and 22.4% of the respondents had high scores on the HADS, indicating anxiety and depression, respectively. In SF-36, respondents had significantly lower results compared to the control group, indicating a lower health-related quality of health.
De Wandele et al., [44]	The total autonomic symptom burden was higher in EDS-HT (57.9 ± 21.57) than in controls (11.3 ± 19.22), especially according to orthostatic and gastrointestinal complaints.

[34] and Nicholson et al. [35] evaluated the correlation of this result with the flexibility of the shoulder joint. Johnson et al. [36] checked the correlation with lower limbs on a group of professional footballers. A different approach was shown by the Nourissat group [37], who tested the truth of the thesis that shoulder dislocations are one of the first clinical symptoms indicative of EDS-HT. In turn, Romeo et al. [38] pointed out the lack of effective diagnostics in children up to five years of age, and assessed the credibility of Beighton's score in relation to such young patients. Palmer et al. [39] and Mannset et al. [40] aimed at validating the Bristol Impact of the Hypermobility (BioH) questionnaire, which was considered more accurate than Beighton's.

EDS-HT is often a diagnostic challenge due to its difficulty in determining etiology and the wide range of symptoms of varying severity. Each of the research groups mentioned above used different, comprehensive EDS-HT diagnostics, or compared the methods used to select the most sensitive and specific.

Skwiot et al. [26] used the Grahame and Hakim questionnaire, which consists of five questions about the incidence of past and present symptoms. The effectiveness of the test is estimated at 82–85% and two positive responses are enough to determine hypermobility of the joints. The second method used was Sachse's criteria which consist of 13 tests assessing three degrees of mobility, where the first – A, is the range from hypomobility to a normal state, B – normal or slightly hypermobile joints, C – hypermobility. To determine excessive mobility, the patient must pass seven tests with a positive result. Tests are based on angles during joint rotation. The authors of the study noticed that the modified Sachse criteria may be particularly useful for the diagnosis of hypermobility in dancers, who constitute a significant group of people surveyed in this respect. This questionnaire draws attention to the mobility of the hips, shoulder girdle and spine in various planes, which was omitted from the Beighton scale. However, they point out that people practicing specific sports that require flexibility, such as dancing, should be subject to different diagnostic criteria. This may be supported by the fact that in their study each of the tests performed gave a different diagnostic result.

Another article related to this issue is the work of Armstrong et al. who assessed the effectiveness of Beighton's result as one of Brighton's main criteria [41]. They are used in the diagnosis of Joint Hypermobility Syndrome (JHS), which was once considered a very similar disease to EDS-HT. Armstrong conducted his research on a group of dancers and footballers. The results obtained and their analysis allowed him to conclude that the Beighton result is an effective predictor of joint pain, as well as their sprains and subluxations.

The Contompasis result used in the work of Schlager et al. [27], in addition to testing joint flexibility as per Beighton's, also evaluates foot flexibility. The maximum number of points in the test is 70, with the cut-off point for hypermobility being 30 or more. Hospital del Mar criteria, used by the same research group, highlight 10 factors: mobility of the thumb, fifth finger, elbow, shoulder, hip, kneecap, ankle, foot (first metatarsophalangeal joint), knee flexibility and susceptibility to injury. Measurements are made only on one, non-dominant side of the body. The maximum number of points in the test is 10, a result above or equal to five indicates the patient's hypermobility. The effectiveness of these criteria is confirmed by the work of Bevilacqua Junior et al., who used

them to determine hypermobility in children under 16 years of age [42]. They considered it a reliable tool for diagnosing excessive joint mobility, but also emphasized the need to set specific thresholds for age and ethnicity.

Birch et al. [28] used the SF-36 questionnaire, which is a validated tool for determining the health and functionality of a patient. With 36 questions in eight categories, it summarizes the mental and physical state of the examined person. The increased risk of depression among patients with EDS-HT due to chronic pain or concomitant diseases is becoming noted more and more often [43]. In this case, SF-36 was used to assess the quality of life of patients after hip surgery. A significantly lower result was observed among the subjects after surgery compared to the control group, especially in relation to physical health, which deteriorates with longer observation time. However, it should be mentioned that the collected data constituting the control came from 1994, which could have influenced the results obtained. No relationship was found between the quality of life and hip joint mobility.

In his work, Cypel [31] pointed out the risk of Beighton's false results in the case of muscle pain or their excessive tension in subjects, as well as ignoring the explicit symptoms of EDS-HT in the case of the patient failing to meet the requirements of this result. He proposed testing the shoulder joint deviation as an alternative method to the current standard. In this test, the examiner puts his right thumb and forefinger on both sides of a subject's left shoulder blade. The examiner's left forearm supports the patient's left arm, which rotates upwards with the elbow flexed. The examiner then passively tilts the patient's shoulder until the shoulder blade begins to tilt. The examiner then measures the angle between the patient's body and his arm with a goniometer. The same procedure is applied to the patient's right arm. The measurement was stopped when the patient reported pain or there was a risk of joint dislocation. Based on the results obtained, the author concluded that people with EDS-HT had a significantly higher shoulder angle deviation, regardless of age, gender or Beighton score, compared to a healthy control group. Whitehead et al. [34] and Nicholson et al. [35] also focused on assessing shoulder mobility. Whitehead et al. [34] checked its correlation with Beighton's score, for which 160 patients were examined for shoulder rotation, deflection and stability. After analyzing the results obtained, the authors of the study unequivocally stated a weak correlation of the Beighton score with the tests checking the mobility of the shoulder joint, because it does not reflect the degree of its mobility.

Nicholson et al. [35] assessed the credibility of a new method for measuring mobility of the upper limb joints, comparing it with Beighton's score and clinical evaluation. In addition, their aim was to identify general hypermobility and determine the cut-off point in its classification. The afore-mentioned new method, called the Upper Limb Hypermobility Assessment Tool (ULHAT), involves assessing the mobility of several upper limb joints in various planes, and includes passive physiology and active range of motion. Therefore, 12 joints which are usually unstable were selected, and cut-off values determined for each one. By conducting studies on three groups (healthy, with hypermobility and undiagnosed in which the disease is suspected), the authors confirmed that ULHAT is a reliable tool for recognizing hypermobility, both upper limb and generalized.

Nourissat's [37] work focused on shoulder dislocation as

one of the first symptoms of EDS. Analyzing clinical and radiological data in terms of recorded hypermobility, injury of vessels or nerves, they identified a group of patients diagnosed with EDS, not older than 14 years, whose dislocations of this joint occurred more often and appeared earlier. It was also noted that they were more likely to experience dislocation pain after dislocation rather than during it. Radiographs did not reveal any bone defects. Interestingly, there were no differences between the groups in the study of external shoulder rotation. The authors concluded that joint mobility may be a factor suggesting EDS, but it is not a prerequisite. However, it should be remembered that the article does not state which particular EDS type had been analyzed.

Children under five years of age are particularly difficult to diagnose because no reference data on cut-off point for this group are available. Romeo et al. [38] tried to solve this problem by applying the Beighton score to pre-school children. The studies revealed that a score above four is a sufficient cut-off point because 7% of healthy children and 89% of children with genetic disorders indicating hypermobility met this condition.

The last test discussed is the Bristol Impact of Hypermobility (BIOH) hypermobility questionnaire, which Palmer et al. [39] and Manns et al. [40] mention in their articles. This is an alternative to SF-36, the results of which are considered by physiotherapists to be divergent with the aims of physiotherapy. BIOH is designed to better assess the broad impact of hypermobility on the patient's functioning. Palmer et al. [39] stated in their work that BIOH is a reliable test, and a year later the same research team, i.e. the work of Manns et al. [40], reported confirmation of its effectiveness in the assessment of both patients and physiotherapists, and the desire to add it to the standard in the diagnosis of joint mobility.

It is also worth mentioning that one of the main symptoms of EDS are vascular disorders. Therefore, the aim of Celletti et al. [30] was to investigate the autonomic cardiovascular system in patients with EDS-HT. They conducted a set of tests, including deep breathing, the Valsalva maneuver, Early Heart Rate Response to Standing Up (examines the chronotropic response of the heart), grip test (in relation to pressure), and head-up tilt test. When assessing deep breathing, the heart rate range was calculated as a measure of parasympathetic reactivity, and the Valsalva manoeuvre as a sympathetic vascular peripheral response. The head-up tilt test allowed assessment of the cardiovascular system when standing up. The results of the study confirmed the dysfunctions of the autonomic cardiovascular system, and indicated increased sensitivity of baroreflex as one of the symptoms of the disease.

De Wandele et al. [29] checked the degree of dysautonomy in patients with EDS-HT by determining the overall index of autonomic nervous system activity at rest (based on a correlation between heart rate variability and baroreflex sensitivity analysis) and autonomic reactivity. In addition, they conducted a series of studies on factors accompanying dysautonomy, such as reduced physical activity or skin stretch. Autonomic reactivity testing was based on four tests reflecting the dysautonomy level of adrenergic, vagus and sudomotor nerve. The studies mentioned in the work of Celletti et al. [30] were also carried out, i.e. the Valsalva manoeuvre or the head-up tilt test. The degree of flexibility of connective tissues was assessed based on the Beighton score and skin stretch. Subjects also completed questionnaires

about depression and anxiety, habitual physical activity, pain and neuropathic symptoms. Based on the conducted research, it was found that patients with EDS-HT had dysautonomy, probably caused by neuropathy, extensibility of connective tissue and vasoactive drugs.

In another work by De Wandele [44], the authors studied the level of autonomy of people with EDS-HT using a series of studies called the Autonomic Symptom Profile (ASP). ASP evaluates orthostatic, secretomotor, urinary tract, gastrointestinal, pupil, vasomotor, reflex syncope and sleep functions. In addition, they performed a series of tests assessing quality of life and disease burden (including a 5-point hypermobility questionnaire or a pain questionnaire). The obtained results allowed them to state that orthostatic and gastrointestinal symptoms are common in patients with EDS-HT.

As the De Wandele [44] group has already noted, one of the symptoms of EDS-HT involves problems with the digestive system. Menys et al., [32] performed magnetic resonance imaging to assess gastric emptying, its motility and accommodation in the group of patients with EDS-HT with dyspepsia. The results were based on two independent opinions of observers. According to the data obtained, people with EDS-HT have significantly reduced gastric motility. In addition, the article by Kovacic et al. draws attention to people with functional gastrointestinal disorders and hypermobility of joints, and recommend that patients with comprehensive gastrointestinal symptoms should be further examined in this direction [45].

Patients with EDS-HT also often complain of fatigue and poor quality of life [46]. The purpose of the work of Gaisl et al. [33] was to assess the incidence of obstructive sleep apnea in this group, which produces symptoms similar to the above. Therefore, they performed a level-3 respiratory polygraphy, consisting of recording parameters during sleep and evaluated the frequency of obstructive sleep apnea and its impact on the quality of life among patients with EDS-HT. It was noticed that the incidence of this disease is higher in people with EDS-HT than in the control group.

Based on the above-mentioned articles, it can be concluded that the cooperation of doctors from various fields may allow for a comprehensive, probably faster and more accurate diagnosis, and thus more effective treatment.

CONCLUSIONS

In order to diagnose such a complex condition as EDS-HT, one should be guided not only by the established standard which is the Beighton score, but also by additional tests that would confirm diagnostic decisions and reduce the risk of error. According to the Ehlers-Danlos Society, EDS-HT is determined by the Beighton score, skin stretch and wound healing assessment, family history and other tests that the doctor considers appropriate [47]. Although the Beighton score still remains the most important diagnostic method and the one most commonly used, the extension of diagnostic tests with additional criteria, including those presented in this literature review, would allow reduction in false diagnoses, and result in better and perhaps earlier diagnosis. This is very important from the perspective of implementing appropriate treatment and the mental comfort of the patient.

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