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Generalised joint hypermobility as a symptom of chosen diseases and syndromes

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Abstract

Introduction: Hypermobility is defined as ability to actively or passively perform a move, which exceed the norm for range of movement for each joint. In any case of hypermobility it is crucial to determine if it is a sign of pathological process. Join hypermobility is a frequent abnormality in a general population and may be caused by a numerous genetic disorders.

The aim of this paper is to compare the most important diseases which may manifest in generalized joint hypermobility.

This study include available knowledge about hypermobility in particular diseases and syndromes which are: Joint Hypermobility Syndrome, Ehlers-Danlos Syndrome Hypermobility Type, Marfan Syndrome, Loeys - Dietz Syndrome, Down Syndrome, Fragile X Sydrome.

Key words: hypermobility, Ehlers-Danlos Syndrome, Marfan Syndrome, Loeys-Dietz Syndrome, Down Syndrome, Fragile X Syndrome

Introduction

Generalised joint hypermobility (GJH) is defined as ability to perform active or passive movement exceeding the norm for range of motion in all or some joints [1].

Hypermobility may be present in diseases such as Ehlers-Danlos syndrome, Marfan syndrome, Osteogenesis imperfecta, Benign Hypermobility joint syndrome (BHJS), a Loeys-Dietz or Down syndrome, Fragile X syndrome or Klinefelter syndrome [2,3].

Hypermobility may affect one or many joints. To evaluate the range of hypermobility the Beighton score is used. It takes into consideration the hypermobility features such as hyperextension in the elbows, knees, metacarpophalangeal of (MCP) fifth finger of the hand, passive adduction of the thumb to the inside of the forearm and bending the torso forward to the point of touching the floor with one's hands. Maximum score is 9, while the Hypermobility is defined as a result of ≥ 4 [3].

Moreover, in each case of hypermobility other symptoms may be present, which could indicate the presence of serious diseases. If the result of Beighton score indicates the presence of HW, the criteria of Brighton score should be applied to differentiate the BHJS from plain hypermobility [3]. This score takes into account the accompanying symptoms such as pain, history of musculoskeletal injuries, soft tissue rheumatism, marfanoid habitus, skin abnormalities, eye signs, varicose veins of the lower limbs, hernias and vaginal or anal prolapse.

Research conducted on preschool children showed the presence of hypermobility (defined as a >4 points on a Beighton score) in 22 out of 284 healthy children (7%) and in 23 of the 26 children with genetic diseases associated with hypermobility (89%), which may indicate that hypermobility is a symptom often associated with genetic diseases [4].

In clinical Hypermobility joint pain is often present: among nearly 200 children with Beighton score 5 up to 12.3% presented joint pain [5]. Furthermore, children who experienced joint pain of unknown etiology in up to 66% presented hypermobility [6]. It is also proved that hypermobility which causes no symptoms at all occurs in 4% to 13% of the population [7,8]. It is observed in approximately 5% of women and 0.6% of men [9,10]. It should be noted that hypermobility is not a disease, but only a symptom and its presence depends on age, gender and race (it is more common in children, women, and in Black and Asian races) [2].

Hypermobility may also be acquired. It has been shown that some activities and sports can increase range of motion of joints [1,11].

The pathophysiology of the hypermobility lays in disproportion between quantity of type I and type III collagen. The type I collagen has the highest tensile strength, and it is the most frequent type found in the body. It is present in tendons, joint capsules, skin, bones and nerve sheaths. Type III collagen is much more stretchable and disorganized. It physiologically occurs in organs such as the intestines, the skin and the vessels [2]. Increase of type I collagen quantity relative to type III quantity results in insufficiency of ligament strenght which presents as hypermobility [3].

Early diagnosis is very important especially in children, because the hypermobility can lead to serious and frequent musculoskeletal injury [12]. Particular attention should be paid to children who train sports, as well as those who are beeing recruited to sport disciplines in which hypermobility might be seen as an advantage, which may lead to worsening of hypermobility symptoms, such as swimming or gymnastics. Improper assesment of exercises in children with hypermobility may in time lead to degenerative changes of the joints or even disability [13,14]. Unfortunately, children are only tested for the presence of faulty posture, while the additional test of hypermobility occurence during the clinical examination of the patient would allow to prevent worsening the symptoms of hypermobility in affected children. The purpose of this study is to evaluate the literature and to provide the most current information in the subject.

Description of knowledge

Jhs/Eds-Ht – joint hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type

Joint Hypermobility Syndrome is defined as hereditary disease of connective tissue, characterised by joint hypermobility, often present in multiple joints and musculoskeletal pain, excluding presence of inflammatory joint diseases as rheumatoid arthritis [15]. Ehlers-Danlos syndrome is a clinically and genetically diversificated group of diseases which are characterised by a combination of three main symptoms: generalised joint hypermobility, skin hyperextensibility and tissue fragility. In each type of Ehlers-Danlos syndrome multi-joint hypermobility may be present, but it is most exhibited in classical and hypermobile type, where it can be even manifested as recurring joint dislocations [16]. Clinical image of EDS classical type consists of joint hypermobility, muscle hypotonia, delayed gross motor development and fatigue, whereas hypermobile type consists only of hypermobility and musculosceletal pain, which responds to clinical image of Joint Hypermobility Syndrome [16]. This similarity of

clinical presence suggests that those diseases may be clinically indistinguishable, thus it is recommended to regard them as a single disease entity, at least until molecular research will be able to determine whether this diseases have a common genetic cause [17,18]. The leading symptom of JHS/EDS-HT is joint pain, which is probably derived from overloaded joint surface and/or ligaments [9]. Pain may result in reduction of movement, which leads to muscle atrophy and reduced control over joint. Moreover, impairment of proprioception may happen, probably due to mechanical damage to joint receptors [19,20]. It is worth to remember that occurence of JHS/EDS-HT is associated with mental disorders such as anxiety or panic attacks. There are also papers which may confirm link between JHS/EDS-HT and depression, attention deficit hyperactivity disorder [21,22]. In each case of suspected JHS/EDS-HT it is crucial to thoroughly examine patient to exclude other conditions with similar clinical picture, including vascular type Ehlers-Danlos syndrome, Down syndrome, Klineferter syndrome, Marfan syndrome and Fragile X syndrome [23]. Vascular type Ehlers-Danlos syndrome may be particularly dangerous, as it can manifest in spontaneous arterial, intestinal, or uterine rupture [24]. Clinical features which suggest this diagnosis are: thin, translucent skin, extensive bruising and characteristic facial features [25].

Marfan syndrome (MFS)

Marfan syndrome is an hereditary disorder of the connective tissue caused by mutations in the gene coding fibrillin-1 (FBN1), which is inherited in an autosomal dominant fashion. This disease occurrence varies from 1,5 to 17,2 per 100 000 people, which depends on ethnic group [26]. For example: rather low frequency is noted in Northern Ireland (1.5 per 100,000) and high in China (17.2 per 100,000) [27]. Fibrillin is a glycoprotein which builds extracellular myofibrils and construct tunica media of blood vessels. It's incorrect structure is a direct cause of the decreased ability to endurance stretch, which causes many changes in internal organs. Changes are seen mainly in ocular, cardiovascular and osteo-articular system. The most noteworthy cardiovascular features are dilation of the aortic root and pulmonary trunk. There is also higher risk of vertebral artery dissection. Aortic dissection or sudden rupture of vessel walls are the most common reasons of mortality in this patients [28]. MFS is associated with greater tendency to hernia and stretch marks on the skin [29]. Other symptom which may occur is an expansion of the dural sac surrounding the spinal cord called the dural ectasia [30]. The results of dural ectasia are: low back pain, headache, proximal leg pain, weakness and numbness aroundthe knee, and genital/rectal pain [30].

Person which is affected by MRS manifest extended figure of extremities relative to the trunk (dolichostenomelia) and joint hypermobility. Other skeletal symptoms are: thorax deformities, scoliosis above 20 degrees, limited extension in the elbow joint (<170º), pes planus, hip joint acetabular protrusion, high arched palate, facial dysmorphia.
It is worth noticing that Marfanoid appearance together with arachnodactyly are included in Brighton score criteria.

Loeys-dietz syndrome (LDS)

Loeys-Dietz Syndrome (LDS) is a genetic connective tissue disorder inherited in autosomal dominant manner. It is characterised by aneurysms in the aorta, arterial tortuosity, hypertelorism, and bifid/broad uvula or cleft palate [31]. When LDS was first described, affected patients had a mean life lenght of 26,1 years, with aortic dissection and cerebral hemorrhages as leading causes of death [32,33]. It's occurrence is caused by mutations is genes, which protein products participate in signal transduction after connection of transforming growth factor β (TGF β) and its receptor. It may be mutations in receptor coding genes, as TGFBR1 and TGFBR2 (transforming growth factor β receptor 1 and 2), in ligand coding gene (TGFB2, transforming growth factor β2) and in genes which products are responsible for intracellular signal transduction (for example SMAD3 protein) [34,35]. Generalised joint hypermobility, congenital dislocations of the hip and subluxations of joints may all be symptoms of LDS [36,26]. Even in adult patients with joint laxity LDS cannot be excluded: case report was published, wherein 51 - year old female patient with generalized joint hypermobility had computed tomography conducted, which shown a dilated aortic root, dissection at the aortic arch and significant aortic regurgitation. After carrying out additional tests, she was diagnosed with LDS [37].

Down syndrome

Down syndrome is one of the most frequent chromosome abnormalities in human population. It is caused by trisomy of 21st pair of chromosomes [38]. Frequency is 1 per 600-700 babies born [39]. DS is typically associated with intellectual disabilities and specific appearance, usually slanted eyes, poor muscle tone, a flat nasal bridge, short neck. Down syndrom is commonly manifested with congenital heart diseases, endocrine disorders and increased range of motion in joints. The reason of the joint laxity in these patients is lack of muscle tone and increased flexibility of ligaments, which leads to decrease in proprioception [40,41]. People with Down syndrom were found to often have flattened feet's longitudinal arch, as well

as increased frequency of other defects of lower extremity [42,43]. In some research up to 40 % - 76% Down syndrome patients exhibit hypermobility, but there are papers, which state that it occurs in only 5% of those patients [43,44,45]. Those differences may result of usage of different scores and research methodology, thus more research is needed to properly evaluate this corelation.

Fragile x syndrome (FXS)

The disease is caused by mutation of FMR1 gene which is located on the long arm of X chromosome. Frequency of fragile X syndrome is 1 in 4000 males and 1 in 8000 females [46]. FXS is one of the most prevalent inherited condition of mental retardation [47]. Moreover, specific face features are present. The most common are: long/narrow face, macrocephaly, prominent ears, high arched palate, prominent jaw [48]. EEG anomalies, epilepsy, psychomotor delay, intelectual disability, aggressiveness are other comorbidities. Cardiovascular symptoms include mitral valve prolapse (3-50% of the patients) and aortic root dilatation (approximately 25% of the patients) which can lead to hemodynamic disorders [49]. There are also many orthopaedic aspects of FXS. Numerous patients with FXS suffer from connective tissue disorders, which manifest by hypermobility of interphalangeal joints, pes planus, spinal deformities, skin elastin abnormalities [48]. An connective-tissue disorder involve irregularity of the elastin structure, lack or incomplete arborealisation of elastin in the papillary skin layer and reduced number of elastin fibers in the deep skin. The study conducted in Children's Hospital, Denver, Colorado on 150 male patients with FXS shows the occurance of excessive laxity of the joints (57% of the patients), flat feet (50%) and scoliosis (15%) [47].

Conclusions

Generalised joint hypermobility is a frequent abnormality in a general population. It is worth to remember that early diagnosis and adequate exercise program alows the patients suffering from hypermobility to prevent most of injuries and ease the symptoms. Joint hypermobility may be caused by a numerous genetic disorders, thus knowledge of their clinical apperance is crucial in order to successfully conduce the differential diagnosis in any case of the GJH.

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