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Original article

Developing new classification criteria for diffuse idiopathic skeletal hyperostosis: back to square one

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Abstract

Objective. To revise the definition of DISH and suggest a classification that may better represent our current knowledge of this entity allowing earlier diagnosis.

Methods. Seven rheumatologists and an orthopaedic surgeon suggested a list of 63 parameters that might be included in a future classification of DISH. Participants rated their level of agreement with each item, expressed in percentages. In a second session, participants discussed each item again and re-rated all parameters. Thirty items that were granted $\geqslant$50% support on average were considered valid for a third round. A questionnaire listing these 30 items was mailed to 39 rheumatologists and orthopaedic surgeons worldwide with a request to answer categorically if they agreed on an item to be included as a criterion for a future classification of DISH. Items were regarded as perfect consensus when at least 95% of the respondents agreed and were regarded as consensus when at least 80% agreed.

Results. There was perfect consensus for 2 (6.7%) of the 30 parameters and consensus for another 2 parameters. These items were ossification and bridging osteophytes in each of the three segments of the spine and exuberant bone formation of bone margins.

Conclusion. At present there is no agreement about the inclusion of extraspinal, constitutional and metabolic manifestations in a new classification of DISH. Investigators with an interest in this condition should be encouraged to restructure the term DISH in an attempt to establish a more sophisticated definition.

Key words: diffuse idiopathic skeletal hyperostosis, metabolic syndrome, enthesopathy, spine, obesity, osteoarthritis.

CLINICAL SCIENCE

Introduction

DISH is a condition characterized by calcification and ossification of ligaments and entheseal sites. The first description by Forestier, 60 years ago, described the radiological aspects of the condition with its predilection to the thoracic spine but also to the lumbar and cervical sections of the spine [1]. However, no extraspinal involvement or specific clinical manifestations were described in that important early work. The classification most commonly used for DISH today was proposed by Resnick and Niwayama [2–4] in 1976 and required flowing anterolateral ossifications of at least four contiguous thoracic vertebral segments, preservation of the intervertebral disc spaces and absence of apophyseal joint degeneration or sacroiliac inflammatory changes. DISH may be present without any symptoms in affected individuals, although numerous clinical symptoms have been described, including pain, limited range of spinal motion, dysphagia and increased susceptibility to unstable spinal fractures [5]. However, DISH is not limited to the spinal

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column and has been reported to affect extraspinal locations in many instances. This finding was reflected by the newer definition of Utsinger [6], who lowered the threshold for spinal involvement to two contiguous vertebral bodies but required the presence of multiple peripheral enthesopathies to be included in the diagnostic parameters to establish a degree of probability of DISH. It has been suggested that patients who have probable or even possible DISH might subsequently advance to unambiguous DISH as time passes and patients age. The extraspinal manifestations of DISH have been reviewed recently [7]. Additionally, various constitutional and metabolic abnormalities have been reported to be associated with DISH in varying degrees, although their presence is currently not (yet) mandatory to establish a formal diagnosis of DISH.

The current widespread definition of DISH by Resnick and Niwayama seems to apply best to the more advanced stages of the condition, which may frustrate the conduct of basic research into its aetiology, early pathophysiology and treatment aimed at slowing down progression. Clearly there is a need for a revision of the definition of DISH, with incorporation of all of its known manifestations in a classification that may better represent our current knowledge of this entity [8]. An attempt to redefine the classification criteria for DISH, in view of the above-mentioned limitations, is reported in this work.

Materials and methods

A group of clinicians, consisting of rheumatologists and orthopaedic surgeons, with a special interest in DISH convened in an attempt to generate core items considered essential for the development of a new classification for DISH. Bearing in mind that the prevalence of DISH increases with age, it was suggested that a future classification should easily be able to differentiate between DISH and OA. All participants were presented with a comprehensive review of the literature pertaining to the currently known clinical and radiological aspects of DISH. In the first gathering, all participants suggested a list of parameters that, in their opinion, had to be considered suitable candidates for inclusion in a future classification of DISH. The parameters were divided into subgroups of clinical observations, radiological features, laboratory results and associated findings, totalling 63 items. Participants were requested to rate their level of agreement with each item, expressed in percentages. In a second session, where participants were presented with the results of the first round, the panellists discussed each item again and were requested to re-rate all parameters. Items that were granted $\geqslant$50% support on average were considered valid for a third round (30 items). A questionnaire listing these 30 items was mailed to 39 rheumatologists and orthopaedic surgeons worldwide with a request to answer categorically (either yes or no) if they agreed whether an item should be included as a criterion for a future classification of DISH. Among the 32 responders, 15 were considered experts, based on their peer-reviewed scientific contributions in the field. Items were regarded to have perfect consensus when at least 95% of the respondents agreed and consensus when at least 80% agreed. Expert and non-expert members were compared via χ^2-tests.

Results

The list of the items and their level of support is provided in Table 1. Among the experts there was perfect consensus for 3 (10%) of the 30 parameters and consensus for another parameter (3.3%). Among the non-experts there was perfect consensus for 2 (6.7%) of the 30 parameters and consensus for another parameter (3.3%). Across all the 32 members, there was perfect consensus for 2 (6.7%) of the 30 parameters and consensus for another 2 parameters. Members of the two groups disagreed in their assessment for 5 (16.7%) of the parameters. Some items, not reaching the necessary level of agreement did obtain a high level ($>$70%) of support (items 14, 17, 29 and 30).

Discussion

In this Delphi exercise, agreement for items to be included in a future classification of DISH was achieved for ossification and bridging osteophytes, in each of the three segments of the spine, and for exuberant bone formation of bone margins. A few more items obtained support that did not reach the pre-established level for consensus.

The remaining 26 items, which did not obtain consensus, could be partitioned into four main domains. Domain 1 encompassed mostly symptoms of pain, either spontaneous or provoked, in joints or soft tissues (Table 1; items 5–7, 9, 12); domain 2 included symptoms or signs of stiffness and restricted range of movement (items 8, 10, 11); domain 3 included mainly radiological evidence of ossification of ligaments and/or enthesopathies (items 19–27, 29, 30); domain 4 is composed of associated constitutional and metabolic abnormalities (items 13–18).

Radiographic involvement of all segments of the spine probably obtained consensus because these abnormalities have been extensively reported in DISH, and spinal involvement is a mandatory feature in the present classification. It also denotes that DISH is still perceived by most practitioners as a spinal disease. DISH has also been accepted as a bone-forming condition, particularly because the affected entheses are often extensively ossified. DISH should be differentiated from other conditions that might share with it the features of exuberant new bone formation and enthesopathies, mainly AS and OA. DISH and AS may sometimes co-exist. The distinctive features between these two entities have been recently revised [9]. Briefly, the main distinguishing features of DISH compared with AS are a higher age of presentation, absence of sacroiliac joint erosions, absence of apophyseal joint obliteration, frequent ossification of the anterior longitudinal ligament (ALL), absent enthesopathies with erosions, no association with HLA-B27 and being a relatively mild or even painless disease.

A more challenging task is the distinction between DISH and OA, because both conditions are common in the elderly and their prevalence increases with age.

Table 1 Suggested items for a new classification and their level of support

Item no.	Suggested items (30)	Level of support (all)	Level of support (experts)
1	Exuberant new bone formation	Perfect consensus	Consensus
2	Enlarged bony bridges C-spine	Consensus	Perfect consensus
3	Enlarged bony bridges T-spine	Perfect consensus	Perfect consensus
4	Enlarged bony bridges L-spine	Consensus	Perfect consensus
5	Pain in the T-spine	No	No
6	Shoulder pain	No	No
7	Provoked rotator cuff pain	No	No
8	Restricted shoulder ROM	No	No
9	Provoked pain in patellar enthesis	No	No
10	Restricted elbow ROM	No	No
11	Restricted chest expansion	No	No
12	Disability affecting QOL	No	No
13	Male gender	No	No
14	Diabetes mellitus	No	No
15	Arterial hypertension	No	No
16	BMI $\geqslant$ 30	No	No
17	Obesity	No	No
18	Metabolic syndrome	No	No
19	Enthesopathy shoulder	No	No
20	Enthesopathy elbow	No	No
21	Enthesopathy ilio-lumbar	No	No
22	Enthesopathy hip region	No	No
23	Enthesopathy Achilles	No	No
24	Enthesopathy plantar fascia	No	No
25	Enthesopathy cruciate ligament	No	No
26	Whiskering of ischium	No	No
27	Joint capsule ossification	No	No
28	Absent history of old SNSA	No	No
29	T-spine bridges by CT	No	No
30	Absent sacroiliitis by CT	No	No

QOL: quality of life; SNSA: seronegative spondyloarthropathies.

The differences lie in the pattern of spinal involvement as well as in the peculiarities of apophyseal joint involvement. In DISH the most characteristic site of involvement is the thoracic spine, which is the least mobile portion of the spine, with preservation of the intervertebral height. In OA the most commonly affected sites are the most mobile segments of the spine; i.e. the lower cervical and lumbar segments. The osteophytes associated with spondylosis are usually non-bridging and form horizontally, while the osteophytes in DISH are typically oriented vertically, usually flowing and do not originate from the vertebral body but rather from the entheses, mainly the ALL.

Peripheral joint involvement in DISH has some distinctive features, such as involvement of joints usually unaffected by OA, increased hypertrophic changes compared with primary OA, prominent enthesopathies in sites adjacent to peripheral joints, and calcification and ossification of entheses in sites other than the joints [7].

The items that did not achieve consensus, however, have been reported in the literature to be associated with DISH. But why were they not considered relevant enough to be included in a future classification?

The clinical manifestations of pain and stiffness have not been thoroughly investigated. Pain has been reported in some studies [4, 5], but a controlled study did not reiterate the findings [10]. Furthermore, a recent study suggested that in older men affected by DISH, back pain was even less frequent compared with non-DISH patients [11]. Spinal stiffness as an obvious result of the radiographic appearance can be easily accepted and has been better studied [12, 13].

It has been reported that patients with DISH can develop OA-like involvement in atypical sites such as the ankles, elbows and MCP joints or hypertrophic OA changes [14–16]. However, only a few controlled studies have addressed the correlation between the radiographic changes and clinical manifestations, and these studies yielded conflicting results. For example, hyperostosis of the shoulder has often been associated with shoulder pain [14]. On the other hand, the association of hyperostosis of the elbow and pain was found to be dubious [16]. Therefore the inference that joints and entheses with these radiographic changes would behave clinically like what is expected from damaged joints and soft tissues in other diseases was not convincing enough for the participants to be included in a future classification. The hypertrophic nature of the joints involved should logically lead to the assumption that these joints have limited range of motion (ROM). In fact, reduced ROM in peripheral sites

has been described, but studies were uncontrolled or, with a limited number of patients [17].

For many years DISH has been associated with metabolic and constitutional derangements. These abnormalities include obesity, large waist circumference, hypertension, diabetes mellitus, hyperinsulinaemia, dyslipidaemia and hyperuricaemia, which eventually lead to metabolic syndrome and increased cardiovascular risk [18–22]. Some of these associations have been questioned [23]. Other studies raised concerns due to the presence of confounders such as OA and elevated BMI. Only a few studies were performed in keeping with the modern definitions of metabolic syndrome and associated metabolic abnormalities [22]. It is assumed that these metabolic derangements play a role in the pathomechanisms of DISH. The pathomechanisms of DISH are probably related to the thickening and stiffening of entheseal sites of tendons, ligaments and joint capsules. Several factors that might enhance these processes have been reported, including increased levels or activity of insulin, insulin-like growth factor 1, platelet-derived growth factor BB, transforming growth factor β1, bone morphogenetic protein 2 and the Wnt/β-catenin pathway [24]. Larger studies are needed in order to establish the role played by these and other factors on the pathogenesis of DISH. Again, the inconsistencies in the literature did not convince the present study participants to incorporate these items into a future classification.

Large, usually symmetric enthesopathies in various sites have also been reported in DISH [7, 25]. Most of these studies were uncontrolled and reported on a limited number of patients. This could partially explain the mistrust in these features to be included in a new classification. Of note is a controlled study on enthesopathies affecting the pelvis, which showed that the presence of enthesopathies in specific sites could be a good predictor for the diagnosis of DISH [26].

It has been suggested that in peripheral enthesopathies the increased width of affected cortex is so characteristic as to suggest the presence of DISH even in the absence of spinal radiographs [3, 17]. As a result, Utsinger [6] suggested that a possible diagnosis of DISH could be established even in the absence of spinal abnormalities, provided the patients have symmetrical peripheral enthesopathies. It has been assumed that these patients will eventually develop the full expression of the disease. Overall, the participants in this study did not feel that their quality of life was adversely affected by the presence of DISH.

The results of our Delphi exercise lead to the question of the future definition of DISH. One option is to continue to investigate patients with established spinal DISH in large controlled studies. In this approach only patients who are diagnosed based on the current classification criteria (either Resnick's or Utsinger's criteria) will be enrolled. This kind of study will require thorough clinical and laboratory evaluations as well as extensive radiological exposure. Another option is to completely redefine the concept of DISH. This means that peripheral as well as axial, clinical and imaging findings should be incorporated into a new definition of DISH. Under these circumstances, DISH should be considered a condition with a propensity to form new bone in peripheral joints, entheses and the spinal column in the absence of other inflammatory mimicries. It would also imply the consideration of constitutional, demographic and metabolic factors that might promote new bone formation. The end product might enable us to identify patients prone to develop diffuse hyperostotic changes with or without spinal involvement [8]. In conclusion, we failed to reach an agreement about the extraspinal manifestations of DISH. A critical review of the literature might explain some of the inconsistencies in our perception of this condition. Investigators with an interest in this condition should be encouraged to restructure the term DISH. Unfortunately, with respect to establishing a more sophisticated definition of DISH, we are back to square one.

Rheumatology key messages

- At present, DISH remains a condition characterized by exuberant ossification, mainly of the spine.
- A new definition of DISH should incorporate constitutional, demographic and metabolic factors that might promote new bone formation.

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