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ARTICLE

Diffuse idiopathic skeletal hyperostosis – appearance and diagnostics in Hungarian osteoarcheological materials

László Paja[1,2]*, Erika Molnár[1], Brigitta Ősz[1,2], László Tiszlavicz[3], András Palkó[4], Hélène Coqueugniot[5], Olivier Dutour[6,7], György Pálfi[1]

[1]Department of Biological Anthropology, University of Szeged, Szeged, Hungary, [2]Hungarian National Museum, Centre for National Heritage, Szeged, Hungary, [3]Department of Pathology, University of Szeged, Szeged, Hungary, [4]Department of Radiology, University of Szeged, Szeged, Hungary, [5]Laboratoire d'Anthropologie des Populations du Passé, CNRS, UMR 5199 - PACEA, Université de Bordeaux 1, Bordeaux, France, [6]Laboratoire de Paléoanthropologie, École Pratique des Hautes Études, Bordeaux, France, [7]Department of Anthropology, University of Toronto, Toronto, Canada

ABSTRACT Diffuse idiopathic skeletal hyperostosis (DISH) or Forestier's disease appears in different skeletal elements, and usually characterized by the calcification of the right side anterior longitudinal ligament of the spine and by the ossification of entheses and ligaments at extra-spinal sites. Although the etiology of DISH is still unknown, but the presence of it seems to be connected with some metabolic diseases, like type II diabetes or obesity. On the basis of Resnick's criteria, the recognition of DISH is not difficult, but in paleopathology, the osteoarcheological series' different state of preservation may result in diagnostical uncertainty. This paper summarizes the results of the physical anthropological examinations carried out seven osteoacheological series from the Great Hungarian Plain, and points to those osseous alterations, which may be helpful in the diagnosis of DISH. **Acta Biol Szeged 54(2): 75-81 (2010)**

KEY WORDS

diagnostic criteria
diffuse idiopathic skeletal hyperostosis (DISH)
Hungary
hyperostosis
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Diffuse idiopathic skeletal hyperostosis (DISH) or Forestier's disease is one of the metabolic disorders that recognisable in the connective and supportive tissues. Pathophysiologically it is characterized by calcification and ossification of soft tissues, especially ligaments and entheses, and it was first described by Forestier and Rotes-Querol in 1950 (Forestier and Rotes-Querol 1950). Later Resnick and his colleagues investigated the correlation between the spinal alterations related to DISH and extraspinal ossification and calcification findings, and in 1976 published their results (Resnick et al. 1976; Resnick and Niwayama 1976). In the second publication Resnick and Niwayama postulated three criteria for the diagnosis of DISH, these are now widely used in literature, and they may help in differentiation of this disease from other spinal disorders, such as ankylosing spondylitis or spondylosis deformans.

The spine has two anatomopathologic spinal types (Cammisa et al. 1998), Type I is related to DISH. It is characterized by irregular ligament calcification, particularly the anterior longitudinal ligament of the spine. The entire spinal column may be involved, but the most typical sites are the mid-low cervical and the mid-low thoracic vertebral segments, bony ankylosis may develop. Radiologically a special view can be seen, as a result of the non-homogenous calcification a radiotransparent band is visible between the vertebral body and the outer layer of the ligament. The calcification appears usually on the right side of the spine. The left side is typically spared or less involved, which is probably attributable to the pulsating aorta. We have to note that zygapophyseal joint gaps and intervertebral spaces are not affected, the original width of these elements are not usually decreased (Olivieri et al. 2009).

Concerning extra-spinal alterations, bony spurs develop at entheses, the most affected sites are the patellae, calcanei and the ulna's olecranon. Ligament ossification, such as sacro-iliac ligament ossification may results in sacro-iliac fusion. DISH appears more often in males than females, and the frequency increases in individuals over 40 years of age (Olivieri et al. 2009).

Although the etiology of DISH is not clear, but several conditions seems to be associated with the disease. These include obesity, hyperlipidemia, hyperuricemia, hyperinsulinemia and late onset (Type II) diabetes (Burner and Rosenthal 2009). Not only recent population studies or case reports show correlation between obesity and DISH, but paleopathological studies also reported some association between the two diseases. A high prevelance of DISH cases has been recognized in ancient clergymen, and it has been hypothesised that the „monastic way of life" might be a predisposing factor of DISH (Rogers and Waldron 2001; Verlaan et al. 2007). Other paleopathological studies point out that development of DISH has a correlation with higher social status (Jankauskas

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*Corresponding author. E-mail: pajalac2000@yahoo.com

Table 1. List of the examined osteoarcheological series.

Cemetery (abbreviation)	Datation	No. of individuals	References of basic data
Homokmégy - Székes (HSZ)	10-11th c. AD	186	Paja et al. 2007
Magyarhomorog - Kónyadomb MHK)	10-11th c. AD	368	Szigeti 2001
Ópusztaszer - Monostor (OPM)	11-18th c. AD	1089	Farkas (ed.) 1998
Bátmonostor - Pusztafalu (BMP)	12-16th c. AD	3782	Farkas et al. 2004
Óföldeák (OF)	12-18th c. AD	419	Paja 2000
Szeged - Vár (SZV)	14-15th c. AD	641	Ősz et al. 2009
Bácsalmás - Óalmás (BA)	16-17th c. AD	481	Békei 1995, Lovász 2005

Table 2. Osseous alterations of the skeletons diagnosed with DISH and early-stage DISH (eDISH) (+: alteration is present, -: alteration is not present, n: anatomic element is missing, alteration is not recognisable).

		HSZ-47	MHK-217	OPM-926B	OPM-R6	BMP-46	OF-16996	SZV-290	MHK-80	OPM-644	SZV-303	BA-159	BA-173
		male Senium	male Maturus	male Adultus	undet. adult	male Senium	male Adultus	male Ad-Mat.	male Maturus	male Senium	male Mat.	male Senium	male Maturus
right anterior spinal ligament ossification		+	+	+	+	+	+	+	+	+	+	+	+
- complete (no. of vertebrae)		5	7+2	4	4	9	9	5	2+2	2+2	2+2	2	3+2
- not complete (no. of intervertebral gaps)		0	4	0	0	1	0	0	1	2	4	8	6
- number of affected vertebrae		5	13	4	4	10	9	5	5	5	6	10	11
narrowed intervertebral disc space		-	-	-	-	-	-	-	-	-	n	-	-
narrowed zygapophyseal joint space		-	+	-	-	+	+	-	-	-	-	-	-
ossification at vertebral foramen		+	+	+	+	+	+	+	+	+	n	+	+
calcification on vertebral disc surface		-	-	-	+	+	+	+	+	+	-	+	+
enthesopathy	upper limb and girdle	+	+	-	n	+	n	+	-	+	+	-	+
	lower limb and girdle	+	+	+	n	+	n	+	+	+	+	+	+
other ossification	spinal	-	-	-	n	-	+	-	-	-	n	+	-
	extra-spinal	-	+	-	n	-	n	+	-	+	-	+	+
sacroileitis		-	+	-	-	-	n	-	-	-	-	-	-
diagnosis		DISH							eDISH				

2003; Giuffra et al. 2010). In recent populations dysphagia is also found in correlation with DISH in several cases (Oppenlander et al. 2009; Seidler et al. 2009; Miyamoto et al. 2009; Masiero et al. 2010), and increased affinity to fracture of the fusioned spine is also mentioned in the recent medical literature (Westerveld et al. 2009).

Concerning the most frequently used methods in recent populations, the diagnosis of DISH is generally based on radiologic analyses. The widely used diagnostic criteria of Resnick and Niwayama (Resnick and Niwayama 1976) are at least four vertebral bodies' fusion, the preservation of the intervertebral disc, the absence of zygapophyseal and sacroiliac joint changes. According to Arlet and Mazières three involved contiguous vertebrae at the lower thoracic spine is sufficient for the diagnosis (Arlet and Mazières 1985). In the opinion of Julkunen et al. bony bridges between two vertebral bodies in at least two sites of the spine have to be characteristic for DISH (Julkunen et al. 1975). However, another set of criteria, defined by Utsinger as probable DISH, lowered the threshold for spinal alterations to the fusion of three adjacent vertebral bodies, but added the presence of extra-spinal enthesopathies to the diagnostic measures (Utsinger 1985).

In Waldron's opinion the operational definition for DISH in paleopathological analysis means the presence of the ossification and fusion of four adjacent vertebral bodies, which are associated with the ossification of extraspinal entheses and ligaments (Waldron 2008).

Biochemical analyses also carried out to make a proper diagnosis for DISH. Denko et al. demonstrated a significant increase in serum growth hormone, insulin-like growth factor –I and insulin in Caucasoid females diagnosed with DISH. In males only growth hormone and insulin were higher than normal controls (Denko and Malemud 2005; Denko et al. 1996).

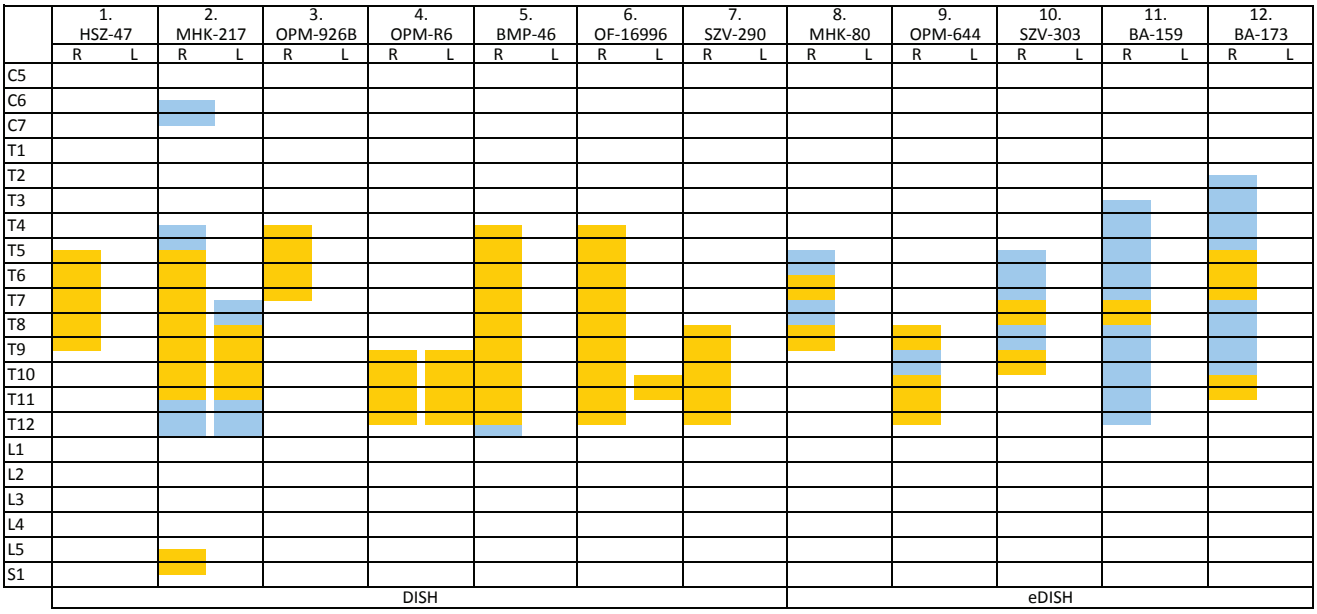

Figure 1. Localization of the complete (orange) and not complete (blue) ossification of the anterior longitudinal ligament in the DISH and early-stage DISH cases (R-right side, L-left side).

Materials and Methods

During our analysis, osteoarcheological remains of seven cemeteries (skeletal remains of 6966 individuals) from the Great Hungarian Plain were examined (Table 1).

During the previously made basic anthropological examinations, determination of sex, estimation of age at death, metric analyses and differenent paleopathological analyses also were done (Table 1).

In our recent study paleopathological anomalies were diagnosed on the basis of macromorphological observations, additionally CT scan was taken and histological examinations also were conducted to support diagnoses.

As for morphological analysis we used a record sheet, on which all of the vertebral and extra-spinal alterations have been recorded. We examined the ligament ossification (size, position, number of completely and not completely fusioned segments), the statement of vertebral articulational surfaces (costal and zygapophyseal facets), the presence and laterality of vertebral bodies' marginal osteophytosis, the statement of intervertebral disc surfaces and any other alterations that might be associated with the development of DISH.

We used the criteria of Resnick and Niwayama (1976); if the intervertebral disc spaces and zygapophyseal joint gaps were close to the original situation, narrowing of these spaces were not visible and at least four vertebral body were completely fused by the calcification of the anterior longitudinal ligament, our diagnosis was DISH. If fewer than four adjacent vertebrae were fused, our diagnosis was early-stage DISH (eDISH). The diagnosis was eDISH also in those cases, where the number of the completely fused vertebrae reached the expected four, but they were separated by intact vertebra(e), or vertebra(e) with calcified, but not completely fused ligament elements.

Concerning radiological examinations, the specimens have been scanned on a GE Lightspeed VCT scan (tube voltage: 120 kV, current: 50 mA) with a 512x512 matrix leading to a voxel size of 0,61 mm x 0,61 mm and a slice thickness of 0,62 mm. Original CT-data were adjusted, and 2D and 3D reconstructions were carried out.

At three specimens from the grave OPM-644 histological analyses were done. The samples from the calcified right-side anterior longitudinal ligament, calcified thyroid cartilage and bony spurs of the anterior patella were partly decalcified (trichloroacetic acid, 5%, 4ºC, 2-3 days) and embedded in paraffin resin. Thin sections (4um) were prepared for histological analysis, hematoxylin and eosin stain was used.

Results

In the material of the examined osteoarcheological series, 7 cases of diffuse idiopathic skeletal hyperostosis (DISH) and 5 cases of early-stage DISH were found, the osseous changes of the affected skeletons can be seen in the Table 2 and Figure 1.

In the first group at least 4 contiguous segments were fused by the ossificationed and calcified anterior longitudinal ligament, the bony bridges were localized on the right side at the anterio-lateral surface of the vertebral bodies (Fig. 1, Fig. 2). Beside this pathognomic phenomenon – except of

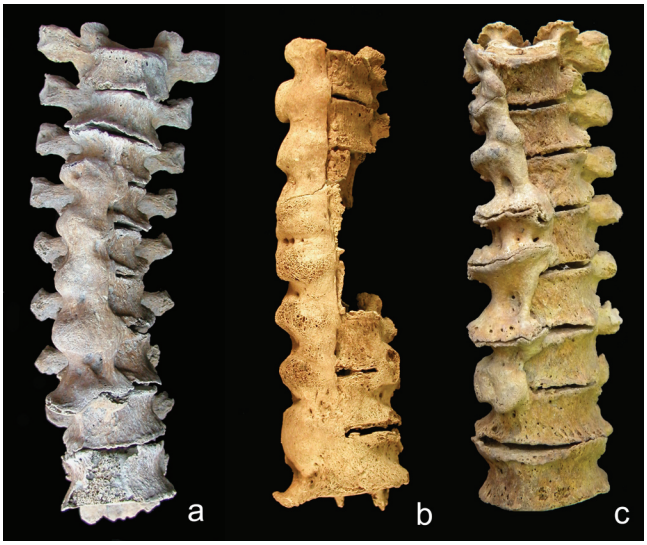

Figure 2. The right side ossification of the anterior longitudinal ligament is pathognomic to diffuse idiopathic skeletal hyperostosis; a: sample of HSZ-47 (male, aged over 60), diagnosis: DISH; b: sample of OF-16996 (male, aged 40-60), diagnosis: DISH; c: sample of BA-173 (male, aged 40-60), diagnosis: early-stage DISH.

Figure 3. Ossification of the spinal ligaments in the sample of BMP-46 (male, aged over 60), a: ossification of the supraspinous ligament; b: bony elements between the two upper facet joints may be caused by the ossification of the ligamentum flavum.

those samples, where the vertebral bodies, as a result of post-mortem changes were not recognisable –the intervertebral spaces were intact in all cases, narrowing or fusions of the intervertebral spaces were not visible. Zygapophyseal joint gaps were also not involved (Fig. 3a), but at the samples of MHK-217, OF-16996 and BMP-46 we found ossified elements of the zygapophyseal joint capsules, these phenomenon confirm our diagnosis for DISH.

In the first group enthesopathies were found at the lower limbs and girdles in all cases, the most frequent sites are the Achilles-tendon insertion of calcanei, and the enthesopathies of the hip bone. The upper extremitties' entheses did not give us such a clear results, in two cases these areas were missing, in one case enthesopathy was not seen at these sites. Calcification of the vertebral disc surfaces appears in four skeletons, at three cases these alterations are not visible. Ossified elements inside the vertebral foramen and between the superior and inferior articular facets of the vertebrae are seen in all of the definite DISH cases (Fig. 3b).

Sacro-iliac ligament fusion can be seen only one case (MHK-217), the post-mortem destroyed unilateral (right side) fusion is associated with unilateral (left side) sacroileitis. In this case, beside the right side vertebral ligament ossification (T4-T12, L5-S1) left side anterior ligament ossification (T7-T12) and complete fusion of the zygapophyseal joint between the L5-S1 segments are also visible. On the basis of the osseous lesions (Olivieri et al. 2009; Olivieri et al. 2007) two different diseases arises in the etiological background, the co-existance of DISH and early-stage ankylosing spondylitis is not disclosed either (Jordana et al. 2009; Paja et al. 2010).

The diagnosis of DISH cases is confirmed by CT analysis as well. The anterior side ligament ossification shows the 'coating phenomenon', the outer part of the ligament appears as a dense layer, the inner part of the ligament is more radiolucent, the shape of the vertebral body did not became squared (Fig. 4c). The vertebral disc spaces and the zygapophyseal joint spaces remained opened, the width of these sites did not became narrow (Fig. 4a, Fig. 4b).

The second group, where the diagnosis is eDISH, includes five cases, bony changes of the affected skeletons can be seen in the Table 2 and Figure1. Although the number of completely fused contiguous vertebrae did not reach the expected four in these cases, special patterns of eDISH are still found (Fig. 1). In four of these cases the number of fused vertebral bodies is at least four, but they are not all adjacent to each other. The other special characteristic is in this group is that the ossification of anterior longitudinal ligament affected at least five vertebrae in all eDISH cases in an incomplete form; in the individuals of BA-159 and BA-173 this number reached ten and eleven, respectively.

Beside anterior ligament ossifications intervertebral disc and zygapophyseal joint gaps with original width are seen in all cases. Lower limbs and girdles' enthesopathies developed in all skeletal remains, in case of upper limbs and girdles, enthesopathies appeared only in one skeleton, in other one case these skeletal parts are missing. Extra-spinal ossification, such as sternal alterations or supraspinous ligament ossification was found in three cases, changes associated with sacroileitis were not seen. Similarly to DISH cases, vertebral foramen changes appeared in all cases, flame-like new bone-formations developed.

The MHK-80 individual's skeletal remains showed some alterations, which may not associated with DISH. Multiple healed fractures can be seen in five ribs, the right clavicle, the

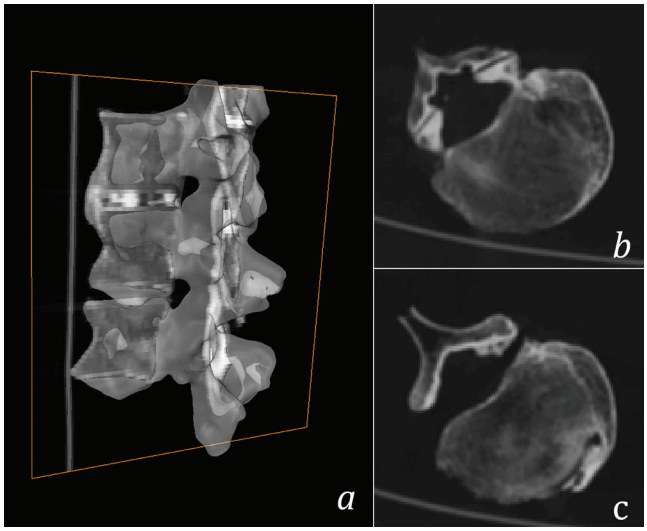

Figure 4. CT reconstructions of the thoracic spine (T9-T11) diagnosed with DISH (sample of OF-16996 - male, aged 40-60,). a: 2D-3D reconstruction of thoracic vertebrae shows unaffected interververtebral disc spaces; b: the zygapophyseal joint spaces are not involved, the vertebral body is not distorted in its shape; c: the ossification of the ligamentum flavum results in exuberant bony spur in the vertebral foramen, the anterior longitudinal ligamentum ossification appears on the right side of the vertebral body.

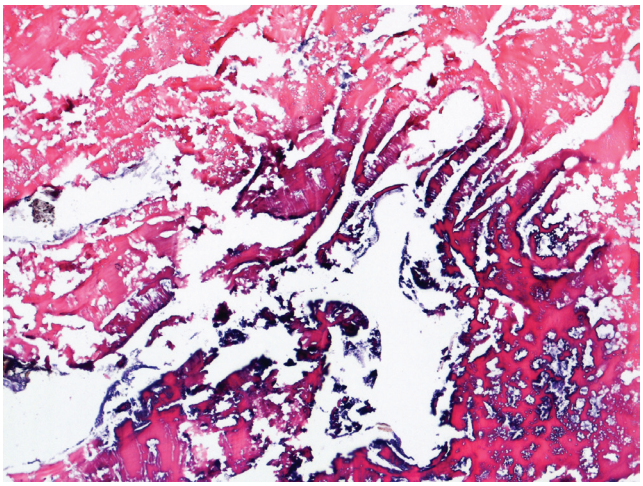

Figure 5. The light microscopic picture of the anterior longitudinal ligament (sample of OPM-644, male, aged over 60) shows normal mature bone structure, but increased accumulation of calcium is seen (hematoxylin and eosin stain, original magnification 10x).

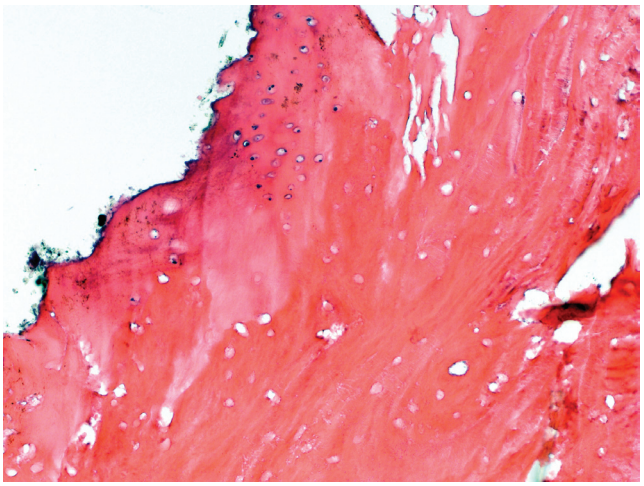

Figure 6. The microscopic picture of the section from anterior patellar spur (sample of OPM-644, male, aged over 60) reveals normal bony structure as well, in some parts, as sign of chondrogen ossification – cartilaginous lacunae are also visible (hematoxylin and eosin stain, original magnification 20x).

right fibula and the left tigh bone. The fracture of the femoral diaphysis healed with disclocation, the cloacal openings and periostal reactions refer to the presence of non-specific infection (periostitis, osteomyelytis). This infection may caused the complete ankylosis of the knee, bony bridges between the femoral and tibial condyles, lytic alterations and proliferative new bone formations are present surrounding the original articulation. However, bony ankylosis of the knee may caused tuberculosis (*Mycobacterium tuberculosis, Mycobacterium bovis*) as well (Blondiaux et al. 1999; Kósa and Tiszlavicz 1999; Thomson and Miles 1921). Although traumatic alterations – especially opened wounds or fractures – favor the pyogenic etiology, but traumatic changes may also reactivate earlier tuberculotic infection (Sauer et al. 2009). Beside lower extremity's alterations lytic lesions can be seen in the first lumbar vertebral arch, the spinous process disappeared, a round-shape, abscess-like lesion of the right lateral process is also visible. These alterations may be caused by pyogenic infection (Carragee 1997; Garcia and Grantham 1960; Nather 2005), but tuberculosis in the background is not disclosed either (Anderson 1940; Moore 1922; Nasser et al. 2002). Summarizing the phenomena, the etiology of these multiple alterations is not clear, further molecular examinations need to carried out.

During our examination, microscopic analyses also were done, samples of the OPM-644 skeleton were examined. The light microscopic picture of the anterior longitudinal ligament (Fig. 5) and thyroid cartilage shows normal mature bone structure, but increased accumulation of calcium is seen. The microscopic picture of the section from anterior patellar spur reveals normal bony structure as well, in some parts, as sign of chondrogen ossification – cartilaginous lacunae are also visible (Fig. 6).

Histological analysis reveals a long-term ossification and calcification process, these data fit to diffuse idiopathic skeletal hyperostosis, where a slowly developing hyperostotic process is present.

Discussion and Perspectives

As a result of our analysis, material of seven osteoarcheological series was investigated. The sample contains remains of 6966 individuals, the fact that the state of preservation of the material greatly varies made some difficulties during the analysis. As DISH is a diffuse disease involving almost the whole skeleton, the presence of lots of skeletal elements is necessary for a more precise diagnosis. In that case, when taphonomic processes results in fragmentary state of preservation, or results in the lack of any part of skeletal remains, the number of definite cases decreases. As a result of the above mentioned facts, statistical analysis was not calculated, prevelance of DISH is not countable in this sample. Connection between DISH and social status of the individuals diagnosed with DISH is not known, detailed archeological data are not present, so association between DISH and higher social status is not examinable.

Concerning Resnick and Niwayama criteria, the differentiation and separation of DISH and early-stage DISH cases seems to be very artificial, the very thin line between the two categories is based on the difference of only one alteration. In those cases, where fusion at least four adjacent vertebral bodies is present, the diagnosis is DISH, while if less than four contiguous vertebrae are fused, the diagnosis is eDISH. Concerning other spinal and extra-spinal alterations there's no difference between the two categories, diffuse ossification and calcification processes are found in all cases of the two categories. Interestingly enthesopathies were not seen in all cases, but ossification in the vertebral foramen (possibly as a result of ligamentum flavum ossification) is visible in all of them. Although the little number of cases does not let to draw unequivocal conclusions, on the basis of these facts diagnostic criteria for DISH and eDISH may need to be reconsidered in the future. In our previous opinion, the diagnosic criteria of DISH in osteoarcheological samples possibly need to be expanded, and some pathologic features (e.g. ligamentum flavum ossification) and patterns (number and relation of vertebrae with complete and not complete fusions) should be taken into account.

Future studies, possibly together with more precise histological, medical imaging and biochemical analyses, needs to be done to investigate the diffuse idiopathic skeletal hyperostosis on three axes:

analyses of the typical lesions, developmental stages, morphological variations and paleodemographical attribute of the definite and early-stage DISH cases;

the co-existance of DISH and other diseases with ligament ossification (ossification of ligamentum flavum and ossification of posterior longitudinal ligament) are present in both medical (Ehara et al. 1998; Epstein 2000) and paleopathological literature (Pálfi et al. 2009). Paleopathological analyses of the associations among these diseases may be helpful in the understanding of these diseases;

paleopathological differential diagnosis of DISH and other diseases (e.g. ankylosing spondylitis, degenerative spinal alterations, infections) can be difficult for many reasons. If more than one disease develop in the same skeleton, differential diagnosis is more complicated, so the more precise differentiation of diseases would be very important.

Concerning these axes, different methods and collaborations need to be used; this pluridisciplinar approach may provide helpful new informations for equally paleopathology, osteology and researchers, who would like to get more information about past populations' health status.

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