Short Communication

Attenuated form of Lysosomal Storage Disease in a Medieval Skeleton from Austria

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Abstract

Introduction: Forty years ago, a medieval skeleton from the 9th century was found near Pitten, Austria. The skeleton’s burial position at the edge of the cemetery, the presence of multiple skeletal changes typical of mucopolysaccharidosis and its similarity to a painting by Virchow 200 years ago have previously been interpreted to indicate Pfaundler-Hurler disease, the early name for mucopolysaccharidosis type I.

Materials and methods: These previous findings were re-evaluated and compared with those for another medieval male skull without lysosomal storage disease but with syphilitic changes. Of special interest was the shape of the skull and face, as well as the typical bony lesions observed in dysostosis multiplex. X-rays of the tibial bones revealed the so-called Harris lines similar to those observed in Morquio syndrome in early reports by Morquio.

Results: Many parts of the skeleton showed signs consistent with dysostosis multiplex: mid-face hypoplasia with a broad nasal bridge, prominent jaw, osteosclerosis of the skull with scaphoid form, elongated sella turcica, signs of premature synostosis of the coronary suture, kyphoscoliosis, platyspondyly with ovoid-like vertebrae and more severe changes in the thoraco-lumbar region, broad iliac wings, severe joint changes in the hypoplastic acetabulae and markedly flat heads of the femoral bones in the varus-position, and shortening of the long bones, thus resulting in a moderate, short stature.

Discussion: On the basis of the individual’s age and current knowledge of lysosomal storage diseases, this young man most probably had an attenuated form of one disease of this group of disorders. The burial of a disabled individual may indicate intellectual disability, as well as severe deficit in vision, hearing or immobility, which are observed in untreated adult patients with mucopolysaccharidoses or several other lysosomal storage disorders.

ABBREVIATIONS

LSD: Lysosomal Storage Disease; MPS: Mucopolysaccharidosis; ML: Mucolipidosis; T: Thoracic Vertebra; L: Lumbar Vertebra

INTRODUCTION

Between 1970 and 1973, in the southern region of Lower Austria in Pitten, near Neunkirchen, a medieval graveyard from the 9th century was found. One of the discovered skeletons (tomb number 126a) was of interest for further investigations [1]. First, its position at the extreme south-eastern edge of the cemetery indicated that the individual had a disease with mental retardation, because such persons were buried without any church consecrations until the 20th century. The second reason for further investigations of this skeleton, which had been examined by X-rays and histological analysis of the epiphyses and growth plates 40 years ago, was the multiple skeletal findings interpreted as a heritable skeletal disease, including multiple changes involving all parts of the skeleton.

The diagnosis was thought to be mucopolysaccharidosis type I, previously described as Pfaundler-Hurler disease. The skeleton was initially classified as a female but was ultimately identified as belonging to a young man between 20 to 30 years of age. The body length was calculated to be 157 cm, which was less than the typical mean body length of adult men in the early medieval time (165.1 – 179.1 cm) [1,2]. Increased knowledge of the skeletal findings recognized as dysostosis multiplex, as well as clinical understanding of patients with attenuated disease courses of lysosomal storage diseases (LSDs), prompted re-evaluation of the initial findings and revision on the basis of clinical experience and scientific knowledge.

MATERIALS AND METHODS

The bones preserved included: the skull, 2 scapulae, the sternum, both clavicles, the complete spine (7 cervical, 12 thoracic and 5 lumbar vertebrae), 12 pairs of ribs, the pelvis and os sacrum, the right and left humeri, the right ulna and
In a study of 78 patients with attenuated Scheie forms of MPS and ML and also alpha-mannosidosis or GM1-gangliosidosis, the radiological findings in dysostosis multiplex and have been identified in 90% of patients with alpha-mannosidosis and in all patients with the adult form of GM1-gangliosidosis with increasing age [13,14].

The vertebral bodies were highly flattened, with a porous-like structure and ovoid-shape in the thoracic spine and with wedge-shaped vertebral from L1-L3, thus resulting in a kyphoscoliotic bending [1,5]. These changes, especially in the region of the thoracolumbar spine (T12), are also characteristic of dysostosis multiplex, thus leading to the thoracolumbar kyphosis observed in MPS patients (Figure 3A and B) [10,11,15]. There is no precise description of the odontoid process of the second vertebra, which is mainly hypoplastic or aplastic in MPS IV (Morquio disease) as well as in others MPS types. The os sacrum in the medieval skeleton revealed signs of spina bifida which might be an additional finding and not related to the genetic skeletal dysplasia.

RESULTS

As described by Szilvássy and Kritschner in 1983, the skull of the young adult male was relatively heavy, owing to excessive bone density (weight 754 grams), with accentuated parietal bones. Via X-rays, a thickening of the skull bones and a flattened elongated sella turcica (‘shoe-shaped’ sella) was observed [1]. The head circumference was 53.2 cm, which was relatively enlarged as compared with the body length. The facial skeleton was relatively small compared with the cranial bones but relatively broad with deeply sunken nasal bones thus suggesting mid-face hypoplasia with a broad nose. There was some frontal bossing as compared with the facial shape of the other male skeleton, as well as a prominent maxillary bone and an even more prominent mandibular bone (Figure 1A and B). This characteristic profile reminded Kritschner and coauthors of a face illustrated by Virchow 200 years ago (Figure 2) [7]. Virchow diagnosed this female patient with cretinism, but in the author’s view, the patient showed a high degree of similarity to a patient with Pfaundler-Hurler disease, the previous name for mucopolysaccharidosis type I [1]. The relatively enlarged head (macrocephaly), thickened cortical bone/calvarium, J-shaped sella turcica and facial anomalies with a broad flat nasal bridge, and obtuse mandibular angle with prognatism are typical radiological findings in dysostosis multiplex and have been observed in several LSDs, in virtually all patients with all types of MPS and ML, and also alpha-mannosidosis or GM1-gangliosidosis [9-11]. In a study of 78 patients with attenuated Scheie forms of MPS, 84-87% of the bone deformities, such as kyphosis, gibbus, scoliosis and hip dysplasias, were found to be consistent with dysostosis multiplex [12]. In another study, dysostosis multiplex was identified in 90% of patients with alpha-mannosidosis and in all patients with the adult form of GM1-gangliosidosis with increasing age [13,14].

The iliac wings are broad, and all pelvic bones have an abnormal shape with flat acetabulae presenting many irregularities in the joint surfaces [1,5]. Both femoral heads showed strong flattening with a spongy appearance, which was interpreted as epiphyseal dysplasia and coxa vara positioning. Although bilateral flattening of the epiphyses of both femoral heads is a constant finding in dysostosis multiplex, several MPS-patients with MPS IVA have normal ilia but poor formation of the acetabular roofs [15].

In general, the long bones of the Austrian male medieval skeleton appeared to be shortened with several open epiphyseal
Figure 2 Early drawing by Rudolf Virchow: Kretin aus Unterfranken. The ‘gestalt’ is reminiscent of a patient with Pfaundler-Hurler-disease (mucopolysaccharidosis type 1).

Figure 3 (A): Vertebral spine with platyspondyly and irregular curvature (kyphoscoliosis). There are more severe changes in the thoracolumbar region as often observed in patients with dysostosis multiplex. – (B) Lateral view of the severely abnormal vertebral bone T12, with an irregular wedge-like anterior part and porous bone structure.

Figure 4 X-ray of the proximal part of both tibial bones. Note the horizontal lines (Harris lines) observed in skeletal diseases with inborn disturbances of osteochondrotic maturation.

plates, thus indicating decreased disproportionate growth and non-simultaneous bone maturation. In X-rays of the long tubular bones (except the humeral bones), Szilvássy and Kritscher have identified so-called Harris lines, numerous transverse lines on the proximal and distal ends in the growth zones of the epiphyses, which were first described by Harris [9]. These radiological changes were interpreted as signs of perturbed ossification of the cartilage cells (Figure 4). Interestingly, the identified lines can be observed in an X-ray from the proximal end of one tibial bone, illustrated in a report from Morquio of a 14-year-old female diagnosed with mucopolysaccharidosis [7]. Multiple defects/erosions and irregular growth plates in the distal femoral and proximal tibial bones have been highlighted in the description of dysostosis multiplex typical for MPS or as the underlying cause for gonarthrosis in other LSDs [10]. Osteoblastic and chondroblastic changes with osteoclastic giant cells and slightly decreased bone mass, as well as disorganized repair around subchondral bone plates, have also been described in ML III alpha/beta [18].

The sternum was separated at the manubrium and three segments of the corpus, and all epiphyses were open. From these four bone fragments, it was not possible to recognize any abnormality generally observed in MPS, such as pectus carinatum or excavatum, which is commonly observed in MPS IV (Morquio disease).

In dysostosis multiplex, the clavicles bones are found to be short and thickened, and the ribs are thickened or paddle-shaped [10]. In the Austrian medieval skeleton, no pathological findings of the clavicles or ribs were identified. This might be a finding inconsistent with dysostosis multiplex, because this discrepancy has also been observed in a retrospective study of 5 patients with MPS IVA and 3 patients with MPS VI in which several patients showed no changes in their clavicles or ribs [15].

Unfortunately, because the investigated Austrian medieval skeleton’s hands and feet were not discovered, they could not provide other typical signs of dysostosis multiplex, such as hypoplastic and irregularly-shaped metacarpal and metatarsal bones [10,19].

**DISCUSSION**

Even skeletons from several thousand years ago can provide
insights into bone pathology and the events that occurred during the life of the individual. One observation in a 5,000-year-old skeleton of a young man found in Pontecagnano, Italy, has revealed signs of double-skeleton trepanation and femur fracture, thus resulting in chronic osteomyelitis [20]. Several archaeological findings from medieval skeletons have provided insights into diseases such as meningoimatosus hyperostosis, as detected in a skull found near the Rochester Cathedral in Great Britain [21]. Three other medieval skeletons found in West-England have provided evidence of erosive peripheral arthritis of different disease-associated origins [22]. In another medieval skeleton from the 11th – early 12th century from the leperosarium cemetery near Winchester, it was possible to isolate DNA of *Mycobacterium leprae* from a young Pilgrim man who suffered from leprosy [23]. In a medieval skeleton from the 13th – 15th century from Estremoz, Portugal, very specific skeletal changes in the vertebral bodies with congenital fusions and division abnormalities have been interpreted as Klippel-Feil syndrome in a man between 30 to 45 years of age [24].

Numerous attempts have been made to corroborate skeletal dysplasias in ancient specimens on the basis of clinical and radiological findings together with present knowledge of genetic diseases and their characteristic signs. Indeed, conditions such as achondrogenesis, achondroplasia, thanatophoric dysplasia, osteogenesis imperfecta and other genetic disorders have been well documented, particularly in recent studies on the collection at the Vrolik museum in Amsterdam [25]. However, even findings of diseases in skeletons from ancient graves are not unique or new. The first illustrations of a possible Maroteaux-Lamy case, another type of mucopolysaccharidosis (MPS VI), were reported by Pachajoa in a collection of pottery from the Tumaco-Tolita culture: these pieces were found on the coast of Colombia-Ecuador and dated between 300 B.C. until 600 A.C., approximately 2,000 years ago [26].

Mucopolysaccharidosis has also been described as one of the differential diagnoses for the humerus varus found in a sub-adult skeleton from a medieval graveyard near Orléans in France [27]. These changes in the femoral head very closely resemble the observations of Legg-Calvé-Perthes disease in bones found in archaeological material in a Langobard cemetery in Moravia and dated from the 5th to 6th century, in which the differential diagnosis of a mucopolysaccharidosis was discussed [28]. In that report, the hip joints were not as flattened as in the presently described skeleton. Parts of an adult skeleton, found in Eunpyeong, near Seoul, South Korea, - from an individual with dwarfism - with many signs of skeletal dysplasia, has provided evidence of a skeletal dysplasia, in which the differential diagnosis of a lysosomal disease has been reported [29].

The Austrian medieval skeleton was found at the extreme south-eastern edge of the cemetery, thus indicating that the individual had a disease with mental retardation. In other early medieval graves, the position of burial appears to be sufficient to conclude the social position of the individual and rites, such as early medieval Muslim skeletons found in the northern areas of the Pyrenees on the Iberian Peninsula [30].

Even in other parts of Lower Austria, there have been discoveries of skeletons thought to present with skeletal signs of mucopolysaccharide diseases. In 2004, in the course of railway construction near the village of Saladorf (Tullnerfeld), a burial field with 28 skeletons from the late Antiquity period (4th century A.D.) was discovered [31]. The age of these findings was estimated on the basis of the simultaneous geological discovery of coins from this time. In this area around Tulln, one of the auxiliary camps of the Roman legions Lauriacum, Vindobona and Petronell-Carnuntum served as a village for smaller units of soldiers. Around this time, the original rite of burning was slowly transitioning to burying the dead with linen shirts and jewelry. Among these 28 skeletons, 5 children younger than three years of age were found. In one of these skeletons of a child younger than six months of age (grave number 1781B), a strongly thickened squama temporalis of the parietal and a thickened mandibular bone suspicious of a mucopolysaccharidosis have been found and compared with bones from Pottenbrunn [2]. The bones from Pottenbrunn in Lower Austria, assigned to the early Middle Ages, included 9 different skeletons of children with a bone pathology interpreted as mucopolysaccharidosis (personal communication and 32). In all these cases, a final diagnosis of MPS I (Hurler syndrome) or MPS IV (Morquio syndrome) could not be made.

In this more than 1,100-year-old Austrian medieval skeleton, there were many signs consistent with dysostosis multiplex, such as a J-shaped sella turcica in a macrocephalic skull with hyperostosis, frontal bossing, mid-face hypoplasia, a prominent jaw, platyspondyly of the spine with ovoid-shaped vertebrae and significantly more pronounced changes in the thoracolumbar region, skeletal involvement with disproportionate growth retardation and severe bilateral Perthes-like changes in the hip joints. Together, these observations led to the diagnosis of skeletal dysplasia associated with MPS, ML and several other glycoproteins, such as alpha-mannosidosis or GM1-gangliosidosis. In all these disorders, attenuated disease courses allow patients to reach an age of several decades. Given the individual’s estimated age of more than twenty years, the author does not agree with the diagnosis of a [Fraundler-] Hurler type of MPS, but instead suggest an attenuated form of lysosomal disorder, for instance of mucopolysaccharidosis. If MPS type I were present, it may have been attenuated Scheie-disease (MPS IS), although these patients with MPS IS often present with micrognathy and no mental retardation. The list of possible differential diagnoses should still include MPS II (Hunter disease), MPS III (Sanfilippio disease), MPS IV (Morquio disease), and MPS VI (Maroteaux-Lamy disease), because all of these conditions may be present in adult patients. Of these, patients with Sanfilippo, the neuropathic form of Hunter’s disease and even the rare MPS VII (Sly disease) or other lysosomal diseases with dysostosis multiplex, such as glycoproteinoses or ML, are associated with mental retardation. But it cannot be excluded, that any other form of severely impaired functions may have developed, stigmatizing the patient to be retarded, from a loss of hearing or visual function, or the immobility that can be expected because of the severe hip changes.

CONCLUSION

Medieval skeletons offer new insights into diseases described long after the individual’s death. Indeed, it wasn’t until 1918, that the Austrian medical doctor Professor Meinhard von Kircher (2017)
Pfaundler presented, together with his colleague Doctor Gertrud Hurler, the first cases of Pfaundler-Hurler disease, later known as mucopolysaccharidosis type IH [33,34]. The original X-rays of these first patients with MPS I, first termed Pfaundler-Hurler disease, show impressive similarities to the presented skeleton from Saladorf, which is, to our knowledge, the first nearly complete skeleton with typical signs of dysostosis multiplex observed for lysosomal storage diseases, especially in the group of mucopolysaccharidoses [35]. Diseases with skeletal changes consistent with dysostosis multiplex and characteristic of lysosomal diseases such as mucopolysaccharidoses, can be carefully classified, documented and even investigated through X-ray analysis, as shown in this skeleton from the early medieval period.

In Austria, a male skeleton more than 1,100-years old was recovered, dating from the early Middle Ages. The many signs of skeletal changes observed in this skeleton showing dysostosis multiplex suggested an underlying mucopolysaccharidosis as well as other entities from the group of lysosomal storage diseases. However, the platyspondyly and very severe changes in the hip joints at the young adult age, the prominent lower jaw and the rather large teeth were highly reminiscent of patients with attenuated forms of Morquio disease (MPSIV).

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CONFLICT OF INTEREST

I declare that I have no financial interest or any other conflict of interest. The reproduction of all figures was in accordance with and with written informed consent from Dr. Kritscher, who generated these photos and X-rays from the medieval skeletons.

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