Review Article

Hip disease in Mucopolysaccharidoses and Mucolipidoses: A review of mechanisms, interventions and future perspectives

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ABSTRACT

The hips are frequently involved in inheritable diseases which affect the bones. The clinical and radiological presentation of these diseases may be very similar to common hip disorders as developmental dysplasia of the hip, osteoarthritis and avascular necrosis, so the diagnosis may be easily overlooked and treatment may be suboptimal.

Mucopolysaccharidosis (MPS) and Mucolipidosis (ML II and III) are lysosomal storage disorders with multisystemic involvement. Characteristic skeletal abnormalities, known as dysostosis multiplex, are common in MPS and ML and originate from intra-lysosomal storage of glycosaminoglycans in cells of the cartilage, bones and ligaments. The hip joint is severely affected in MPS and ML. Hip pathology results in limitations in mobility and pain from young age, and negatively affects quality of life. In order to better understand the underlying process that causes hip disease in MPS and ML, this review first describes the normal physiological (embryonic) hip joint development, including the interplay between the acetabulum and the femoral head. In the second part the factors contributing to altered hip morphology and function in MPS and ML are discussed, such as abnormal development of the pelvic- and femoral bones (which results in altered biomechanical forces) and inflammation. In the last part of this review therapeutic options and future perspectives are addressed.

1. Introduction

Mucopolysaccharidosis (MPS) and Mucolipidosis (ML II and III) are lysosomal storage disorders with multisystem involvement. In MPS, deficiencies of glycosaminoglycan (GAG) degrading enzymes lead to intra-lysosomal GAG storage [1]. In the ML’s, defective trafficking of lysosomal enzymes to the lysosome leads to accumulation of a combination of GAGs and several other complex molecules [2–4].

GAGs are viscous polysaccharides, containing long, unbranched chains of negatively charged amino sugars and uronic acids. The names of the GAGs (hyaluronic acid, dermatan (DS)-, heparan (HS)-, keratin (KS)- and chondroitin sulfate (CS)) describe the precise composition of the polysaccharide chain [5,6]. GAGs are continuously renewed and are modified by several enzymes in the endoplasmic reticulum (ER) and Golgi apparatus [7,8]. GAGs can be formed isolated or are linked to a protein core, a proteoglycan (PG). They form HSPG, CSPG/DSPG and KSPG [7]. These PGs have important functions and can act as adhesion molecules, serpins/proteases, stabilizers, cofactors, and/or co-receptors for growth factors, cytokines, chemokines and regulators of cathepsin activity [5,8]. In the extracellular matrix (ECM) PGs form large complexes with hyaluronic acid, serving as ground substance of connective tissues. In articular cartilage these complexes, in combination with collagen type II fibers, are essential for the integrity and assembly of functional cartilage matrix.

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Articular cartilage is very rich in GAGs containing up to 80% of water, which is important to withstand pressure from outside [5]. Chondrocytes play a crucial role in maintenance of the ECM. Degradation of the components of the ECM (protein fibers, collagen and PGs) by cathepsins and by matrix metalloproteinases (MMPs) is necessary before extracellular GAGs can be transported to the lysosome via endocytosis for further breakdown [5]. Intracellularly, the different types of GAGs are degraded in lysosomes (organelles in the cells specialized in the degradation and recycling of a wide range of macromolecules). At least 11 different enzymes are involved in the degradation of GAGs. The deficiency of each enzyme, results in intra-lysosomal storage of one or more types of GAGs and causes a different subtype of MPS. HS accumulates in MPS type I (OMIM#607014), MPS type II (OMIM#309900), MPS type III (IIA OMIM#252900, IIIB OMIM#252920, IIIC OMIM#252930 and IIID OMIM#252940) and MPS type VII (OMIM#253220). DS accumulates in MPS type I, II, VI (OMIM#253200) and VII. KS accumulates in MPS type IV (IVA OMIM#253000, IVB OMIM#253010), chondroitin 4- or 6-sulfate (CS) in MPS type IV, VI and VII and hyaluronic acid in MPS IX (OMIM#601492) [1].

In the different types of ML’s, ML II (OMIM#252500) and III (ML III α/β OMIM#252600, ML III γ OMIM#252605), the activity of the membrane bound hexamer enzyme UDP-N-acetyl glucosamine-1-phosphotransferase (GlcNAc-PTase, which consists of three subunits, named α2, β2 and γ2), is absent or reduced [9-13]. GlcNAc-PTase is required for the generation of the lysosomal targeting recognition marker, mannose 6-phosphate (M6P), on newly synthesized lysosomal enzymes. Absence or dysfunction of this marker leads to a defective transport of lysosomal enzymes to the lysosome and secretion of lysosomal enzymes. This results in intra-lysosomal accumulation of substrates, such as GAGs and (glyco)sphingolipids [11,14]. The clinical signs and symptoms of ML are very similar to MPS and there is little resemblance to other lysosomal storage disorders.

As with many inborn errors of metabolism, MPS and ML present as a broad clinical spectrum with severely affected patients at one end and very mildly affected patients at the other end of the spectrum.

Intra-lysosomal GAG storage in MPS and ML gives rise to loss of cellular function followed by tissue damage and organ dysfunction [5]. The processes which lead to clinical symptoms observed in the patients all start with 1) intra-lysosomal GAG storage in cells which expands the volume of the lysosomal system and causes dysfunction of the lysosomes (end-stations of the endocytic and autophagocytic transport pathways), followed by 2) abnormal vesicular trafficking, which gives rise to disturbed autophagy and polyubiquitination, 3) loss of lysosomal membrane integrity followed by leakage of proteases (cathepsins) into the cytosol causing apoptosis and dysfunction of the lysosomal membrane ATPase proton pump, which results in a high intra-lysosomal pH which has a negative impact on the function of lysosomal hydrolases (increasing the storage of GAGs), 4) mitochondrial dysfunction [5,15], 5) tissue damage, stimulating an inflammatory response, on top of a process of inflammation induced by activating the toll like receptor type 4 (TLR-4) pathway by GAG storage [5,8,15,16].

All these processes lead to changes of the composition of the ECM (by GAG storage, inflammation, influences on cathepsin activity, and elevated expression of MMPs and unbalanced elevation of MMP inhibitors) [5], and to abnormal production of GAG type specific PGs (aggrecan, syndecan, biglycan and perlecain). These abnormal PGs affect other important processes and pathways in cartilage and bone metabolism [5] for example via interaction with several growth factors, such as bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), the FGF receptor and in the Wnt pathway [5,17].

The characteristic skeletal abnormalities (dysostosis multiplex, craniosynostosis, joint contractures and short stature [18]), which are frequently observed in MPS [1,19] and ML [20-26] are due to intra-lysosomal GAG storage in chondrocytes, bone cells, ligaments and in the ECM leading to dysfunction of these cells and by altered composition of the ECM. This results in reduced quality of cartilage and in the growth plate intra-lysosomal GAG storage in chondrocytes alters endochondral ossification which causes shortening of the long bones [5]. Furthermore bone cell dysfunction disturbs normal ossification which results in thickening and widening of the long and flat bones, and in altered bone remodeling which further impairs the bone structure. The inflammation in the joints in MPS and ML lead to osteo-rheumatoid arthritis and to articular cartilage degeneration. An example of severe osteoarthritis of a femoral head in a MPS II patient is shown in Fig. 1.

The joint which is frequently and severely affected in MPS and ML [25,27-37] is the hip. Hip pathology results in limitations in mobility and pain from young age, and may negatively affect quality of life [38-41].

The aim of this review is to give a comprehensive overview of the current knowledge of the pathophysiology of abnormal hip development in MPS and ML. To better understand the underlying process of the abnormalities observed in hip disease in MPS and ML patients, this review will first describe physiological (embryonic) hip joint development and the interplay between the acetabulum and the femoral head. In the second part the current knowledge about the pathophysiology of abnormal hip development in MPS and ML is discussed. We will present a model in which the cascade of pathological events occurring in MPS and ML pelvic cartilage and bones are illustrated. In the last part potential future therapeutic interventions to ameliorate hip disease are discussed.

2. Normal physiological hip development

2.1. Development and growth of cartilage and bones of the hip

The cells involved in hip joint development are mesenchymal cells, chondrocytes, osteoblasts, osteocytes and osteoclasts. Mesenchymal cells are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts and chondroblasts [42]. These cells are important for the two types of ossification processes of bones. Endochondral ossification forms the long bones (e.g. the femoral bone) and intramembranous ossification creates the flat bones, such as the bones of the pelvis. In the endochondral ossification process mesenchymal cells condense and differentiate into chondrocytes forming a cartilage template. The epiphyseal growth plate is formed, which plays an important role in elongation of the long bones [43]. In intramembranous ossification mesenchymal cells differentiate into osteoblasts and finally into osteocytes and produce bone tissue.

Once bone is fully formed, bone turnover depends on well functioning osteoblasts (bone-forming cells), which can differentiate into osteocytes and osteoclasts (bone-resorptive cells).

2.2. Prenatal development of the hip joint, acetabulum and the proximal femur

Prerequisites for normal hip function are: a regularly shaped acetabulum, centered position of the femoral head (resulting in normal forces on the acetabulum), adequate functioning of the vasculature (which supplies nutrition to the hip joint) and normal function of capillary-ligamentous structures and surrounding musculature [44,45].

Hip development has an embryonic stage, fetal stage and a postnatal stage. In the embryonic stage, the femoral head and acetabulum develop from the same primitive mesenchymal cells [44,46]. Complete cartilaginous models of both the acetabulum and femur are already present at week 7 of pregnancy. The acetabulum is formed by condensation of cartilage cells in three primary centers, where precursor cells form the future ilium, ischium and pube [44] (Fig. 2B). At their fusion point, a Y-shaped epiphyseal growth plate (triradiate cartilage) is created (Fig. 2C).

The labrum of the acetabulum is formed at week 7 of gestation by condensation of the components of the ECM (protein fibers, collagen and PGs) [42]. Complete cartilaginous models of both the acetabulum and femur are already present at week 7 of pregnancy. The acetabulum is formed by condensation of cartilage cells in three primary centers, where precursor cells form the future ilium, ischium and pube [44] (Fig. 2B). At their fusion point, a Y-shaped epiphyseal growth plate (triradiate cartilage) is created (Fig. 2C).
ossification of the femur begins, and this process is complete at 18 weeks of pregnancy. Ossification of the primary centers of the pelvic bones occurs at about the same time (Fig. 2B). The formation of the joint space is completed, and the articular surfaces of both the femoral head and the acetabulum are covered with mature hyaline cartilage (articular cartilage) [44] (Fig. 2). The acetabulum and the labrum continue to develop throughout intrauterine life by growth. The labrum (fibrocartilage) forms the outer margin of the acetabulum [44] (Fig. 2A).

2.3. Postnatal development of the hip joint

At birth, the femoral head is positioned in the acetabulum [46]. During childhood, the widening of the acetabulum is initiated by endochondral growth from the triradiate cartilage and by intramembranous ossification from the primary and secondary ossification centers [47]. The depth of the acetabulum is the result of epiphyseal growth of the acetabular cartilage and the labrum (Fig. 3) [48]. Secondary ossification centers in the acetabulum and the other bones of the pelvis are formed during adolescence (see for details Fig. 2) [44].

Normal pressure of the head of the femur on the acetabulum is necessary for acetabular growth and development. Vice versa, proper positioning of the femoral head in the acetabulum is necessary for adequate growth and development of the femoral head [44,49]. The head of the femur and greater trochanter enlarge by appositional growth. Expansion through three growth zones in the proximal femur (the longitudinal growth plate (LGP), the trochanteric growth plate (TGP) and the femoral neck isthmus (FNI)), determines the shape of the proximal femur (see for details Fig. 3A) [44]. The LGP is responsible for the longitudinal and lateral width growth of the femur and the femoral neck [44]. The TGP elongates and widens the femoral neck. The TGP is a traction epiphysis which needs a physiological stimulus, provided by the pull of the abductor muscles (attached at the greater trochanter), to grow proximally and laterally [49]. The FNI contributes to the lateral width expansion of the femoral neck.

The contact pressures exerted on the cartilage of the femoral head through tight enclosure of the acetabulum is needed for the spherical appositional growth of the femoral head. Increased pressure of the femoral head on the acetabulum, as it occurs for example in developmental dysplasia of the hip (DDH), inhibits the growth of the medial part of the femoral head [44]. This results in the abnormal shape of the femoral head. As a consequence the femoral head subluxates and induces abnormal inhibitory growth pressure on the outer border of the acetabulum. Valgus position of the femoral neck occurs, as a result of the abnormal growth of the femoral head [49] (Fig. 3B). Lack of interaction

Fig. 1. Severe osteoarthritis of a femoral head in a MPS II patient. At the top left site a MRI image of the left femoral head of a 26 year old MPS II patient is shown. There is severe osteoarthritis and abnormal ossification (cartilage remnants) (white stars), which are also observed in the surgical removed femoral head of this patient. Severe loss of articular cartilage is indicated by a white arrow head. In the middle tissue sections of the articular cartilage of the femoral head stained with periodic acid–Schiff (PAS) are shown. PAS stains polysaccharides for example glycoproteins and GAGs. The section at the top is taken from the area in the white box of the femoral head represented at the left. It shows that part of the alignment of the articular cartilage are still intact (orange square), while articular cartilage is lost on the right site (brown square). The section in the middle shows a magnification of the brown square area. The black arrow points to an island of cartilage tissue, which has been formed at a location where bone tissue should be present. At the bottom a magnification of articular chondrocytes. The increased PAS staining in these chondrocytes (black arrows), reflects the intra-lysosomal GAG storage.

At the right section articular cartilage of the same patient is stained with Safranin O (the reddish orange stained areas reflect the cartilage ECM). On top a section of intact articular cartilage (taken from the orange square in the top middle section). The normal ECM is marked with a black arrow. In the middle articular cartilage taken from a damaged area. In this area staining of the ECM is variable and less (circles) indicative for osteoarthritis with some irregular formed island of cartilage. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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between the femoral head and the acetabulum causes secondary deformities of the acetabulum, femoral neck and head.

3. Pathological hip development in MPS and ML

Hip disease in MPS and ML often starts with abnormal early development of the acetabulum and os ilium and, later on, abnormalities of the femoral head.

3.1. Early onset of hip disease in MPS and ML

As GAG metabolism in MPS and ML is already altered in utero, it is hypothesized that the process of GAG accumulation, cell and tissue dysfunction commences during fetal life. This hypothesis is supported by the fact that skeletal abnormalities (abnormal bone shape) have shown to be present in the first years of life in some types of MPS and ML [1,21,24,27–29,34,36,50,51]. The beginning of abnormal pelvic bone formation very early in life was confirmed in our study on hip disease in MPS VI. In those patients of whom very early radiographs of the hip were available (around the age of 2 years) we observed hypoplastic basis of the os ilium and shallow and dysplastic acetabulum [33]. Fig. 4 shows four other radiographic examples of early hip disease in two patients with MPS (MPS I (severest form) and MPS II) and two with ML at ages of respectively 10 days, 3 months, 13 days and 3 months old, and two age related healthy controls. All four patients have the same abnormalities of the os ilium and acetabulum as seen in MPS VI. Furthermore in the ML II patient the typical rickets/hyperparathyroidism-like changes, with femoral cloaking, is present [36]. Such early developmental changes of cartilage and bones will have a lifelong effect on body structure and function [5].
3.2. Histopathological and radiological studies in fetuses, children and animals with MPS and ML

Several histopathological and radiological studies have been performed in fetuses, children and animals with MPS and ML.

Histopathological post mortem studies in fetuses and young MPS patients confirm that bone and cartilage structures are already affected early in life. In a study by Beck et al., multiple vacuoles were found in resting chondrocytes of a 24-week old MPS IV fetus [52]. In another study a transiliac bone and cartilage biopsy from a 30-month old MPS I (severest form) patient revealed an irregular and disordered growth plate of the iliac crest [53]. Fundamental defects in the structure and orientation of chondrocytes in the growth plate were also observed in biopsies of children with MPS I, III and ML II between 0 and 8 years old [54–57]. Other abnormalities that were found at birth in ML patients, that are illustrative for altered bone formation, are the absence of metaphyseal and primary trabeculae and the presence of vacuolated osteoblasts and osteocytes [24,34]. The finding of abnormal pelvic bones with hip luxation in a 30 month old ML III α, β patient further substantiates this assumption [58].

In animal models with MPS VI and VII intrauterine abnormalities in bone development, with severe disorganization of the growth plate, have also been found [59–61]. In a MPS VII mouse model, intra-uterine abnormalities in the epiphyseal growth plates and delayed ossification of the primary and secondary centers (POC, SOC) in tibia were observed. The delayed ossification is suggested to be caused by dysfunction of the chondrocytes which become hypertrophic due to GAG accumulation. These chondrocytes normally stimulate invasion of vascular endothelial and osteogenic progenitor cells into the POC and SOC centers, which is important for calcification of the matrix [62].

4. Pathological acetabulum development in MPS and ML

Acetabular dysplasia is frequently observed in all types of MPS (with exception of MPS III) and ML II and III patients [25,27–34,36,37,51,63] (Fig. 4). In most infants with MPS and ML the acetabulum is shallow and small, while the slope of the acetabulum is still normal (MPS I, IVA and VI patients) [27–29,31,33]. At this stage, there is still full coverage of the femoral head by acetabular cartilage and the labrum (cartilage anlage, see for details Fig. 2A) [64,65]. In MPS and ML the acetabular slope increases over time, finally resulting in a very steep acetabulum (Fig. 5) [27–29,33]. This changes the mechanical interplay of the acetabulum and the femoral head, ultimately resulting in femoral head complications as described below (Fig. 5). The dysplasia of the acetabulum is most likely caused by the abnormal shape of the os ilium, which constitutes two fifths of the acetabulum (Fig. 2). The other bones that embryonically contribute to the acetabulum, the os ischium and os pubis, are normally shaped. The role of the os ilium mal-development in acetabular dysplasia is confirmed by a study of Borowski, who obtained two-dimensional CT scans of the acetabulum of MPS IVA patients, showing abnormalities of the anterior acetabular wall and the roof of the acetabulum. These are the parts of acetabulum that are derived from the os ilium during fetal life [66].

5. Pathological femoral head and neck development in MPS and ML

In contrast to the acetabulum, the femur is relatively normally shaped at birth in most MPS and ML patients and morphological abnormalities develop over time. An important cause of the progressive abnormalities of the femoral head in MPS and ML is the dysplastic acetabulum which is too small for the normal sized femoral head (Fig. 3, [49] and Fig. 5).
Pressure of the femoral head in the acetabulum is important for the acetabular bones to form the cup-shape of the acetabulum. The loss of femoral head-acetabular congruity puts eccentric pressure on the articular cartilage, resulting in adaptive deformity of both the acetabulum and the femoral head [49]. When the medial acetabulum does not receive pressure of the femoral head, it undergoes unrestricted growth leading to an abnormally wide acetabular floor [49]. In contrast, abnormal pressure of the femoral head inhibits growth of the outer border of the acetabulum. The combination of lateral inhibition and medial expansion of the acetabulum results in an increased slope of the acetabulum, leading to migration and can ultimately result in subluxation of the femoral head (Fig. 5). The acetabular deformity puts pressure on the articular surface on the medial part of the femoral head, inhibiting medial growth and allowing unrestrained lateral enlargement. This results in flattening and enlargement of the femoral head (Figs. 3 and 5) [49]. Lateral growth of the femoral head changes the angle of the femoral neck to a valgus position. This process of adaptation of the femoral head (neck) to the dysplastic acetabulum is observed in the MPS I (severest form), IVA, in a subset of MPS II and VI patients [27–33] and in ML II and III patients (Fig. 5) [34,36].

5.1. Pathological ossification of the femoral head and greater trochanter in MPS and ML

In MPS IVA and VI, the ossification of the femoral epiphysis develops differently over time compared to the other MPS patients, as failure to convert cartilage to bone has been observed. This has also been described in ML III α, β patients (Fig. 6) [33,67,35], but not in ML III γ patients [68,69].

The abnormal and delayed ossification of the chondrocytes is observed in the proximal femoral epiphysis, which results in fragmentation of the capital femoral epiphyses (Fig. 5), mimicking multiple epiphyseal dysplasia (MED) [67]. This abnormal ossification has also been observed in the greater trochanter, resulting in fragmentation and underdevelopment of the greater trochanter (Fig. 6). Abnormal angulation of the femoral neck can develop over time, due to the abnormal shape of the greater trochanter. Furthermore, in MPS IVA patients the occurrence of un-ossified cartilage at the proximal lateral portion of the tibia has also been described [70].

MPS IVA, VI and ML II/III patients have in common that they all accumulate chondroitin sulfate (CS) in contrast to the other MPS patients. It could be that CS induces this abnormal ossification of the
chondrocytes. Kudo et al. observed that CS inhibits bone-specific alkaline phosphatase (BAP) in a chondrocyte cell line [71]. Osteoblasts synthesize this enzyme, which is involved in the calcification of bone matrix. Inhibition of this enzyme by CS could explain the ossification abnormalities observed.

Illustrations of proximal femoral head epiphyseal and greater trochanter abnormalities are shown in Fig. 6. It shows hip x-rays of two MPS IVA, two MPS VI patients (sibs), two ML III α, β patients (sibs) and MRI images of the hip for the two MPS VI patients.

In our study of hip disease in MPS VI we noted that in all patients proximal femoral head epiphyseal abnormalities are observed, independent of disease severity. However we also found that the final shape and angle of the femoral heads may differ substantially between patients [33] (Fig. 7). The etiology of this large variation is not understood. Potential influencing factors are environment (life style), secondary genetic factors, ethnicity, differences in quality of cartilage or different chondroitin and dermatan sulfate levels. Our study illustrated a potential genotype-phenotype relationship between specific mutations and hip morphology, but larger studies are needed to confirm these differences [33].

5.2. Pathological femoral head development in MPS III, avascular head necrosis (AVN)

MPS III patients usually express different hip pathology compared to the other MPS types. The abnormalities may include a mild shape anomaly of the acetabula [72,73]. In these patients an entirely different complication may be observed, namely osteonecrosis of the epiphysis of the proximal femoral head. This specific complication has been noted in 22–24% of patients in two small cohort studies [72,73]. The exact mechanism of osteonecrosis is unknown. Potential contributing factors could be inflammation caused by high levels of undegraded HS and/or by avascular necrosis of the femoral head caused by vascular impairment. It is known that in infancy (before bony centers appear), the growth plate of the articular cartilage of the femoral head is nourished in two ways, by diffusion (synovial fluid) and via the bloodstream through the vessels [49]. To reach the growth plate, blood vessels have to migrate through the large volume of cartilage that surrounds it, making them vulnerable to injury [49]. HS has an important regulatory role in endothelial signaling, with high levels of HS found in vasculature [74]. Critically, HS modulates endothelial cell functions, including mediation of leukocyte trafficking, inflammation, angiogenesis and vascular permeability [75]. HS accumulation may dysregulate these processes, causing impaired circulation of the femoral head and ultimately avascular necrosis.

![Fig. 6. Ossification abnormalities of the proximal femoral head and greater trochanter in MPS IVA and VI patients. At the left x-rays of hemi-pelvises of a healthy control are shown taken at ages of 2 and 8 years and at the right, aged matched x-rays of MPS IVA (two different patients), MPS VI (two siblings) and ML III α, β patients (two siblings). In the middle next to the x-rays of the MPS VI siblings, aged matched MRIs of the pelvis of these siblings are shown. Ossification abnormalities (indicated by a white arrow) of the proximal femoral head and greater trochanter (stars). Images were obtained from patients followed at the Center for Lysosomal and Metabolic diseases at the Erasmus MC University Medical Center Rotterdam with consent of the parents.](image-url)

![Fig. 7. Femoral head abnormalities in MPS VI patients. X-ray of hemi pelvis at age 14 of one healthy control and three different MPS VI patients. Each patient has a different shape of the femoral head and angulation of the femoral neck. Pt.; patient, SP; slowly progressive, RP rapidly progressive [33].](image-url)
6. Differences in hip disease between patients with MPS and ML and patients with developmental dysplasia of the hip (DDH), and avascular osteonecrosis (AVN)

MPS and ML II/III patients are frequently misdiagnosed with DDH before the diagnoses MPS and ML is made.

There are important differences of the shape of the acetabulum and femoral head between MPS and ML patients and patients with isolated DDH and AVN. Knowledge of these differences can aid in accurate discrimination between these three different types of etiologies of hip disease. Establishing the etiology is vital to determine the optimal treatment for the patient and the prognosis. In DDH the acetabulum is typically shallow, lateralized and anteverted, with deficient coverage of the femoral head at the anterior, lateral and superior site. The femoral head is small compared to the acetabulum, there is excessive femoral neck anteversion and the femur neck is short with an increased neck shaft angle [48]. In contrast, the femoral head in the MPS and ML patients is large compared to the dysplastic acetabulum (Fig. 8). Hip ultrasound is recommended in infants younger than 4 months for screening for DDH [76]. With this method diseases like MPS and ML can be easily missed for example by difficulties in anatomical interpretation [36] and it would be preferable to use other imaging modalities like hip x-ray and or MRI.

In avascular necrosis, not related to MPS and ML, the necrosis is often present at the lateral site of the femoral heads (Fig. 8). In MPS abnormal ossification of the epiphysis is characteristically observed at the central and medial part of the femoral head [33]. Bilateral ossification abnormalities in the proximal epiphysis, which may mimic avascular necrosis, are typically found in MPS IVA, VI, VII and in ML III and should trigger suspicion of the diagnosis for these conditions.

Imaging modalities other than hip x-rays to achieve earlier diagnosis for patients with MPS and ML are MRI and computed radiography (CT) (not preferable in the pediatric population).

7. Clinical consequences of hip disease in MPS and ML

In all types of MPS and in ML patients a combination of factors such as inflammation, triggered by GAG accumulation [16,77], disturbed biomechanical forces on deformed bones and joints and reduced quality of cartilage, are responsible for the joint destruction and osteoarthritis. In addition, failure of epiphyseal ossification may lead to fragmentation of the proximal femoral head and to early secondary osteoarthritis, which has been described in MPS IV, VI, VII and ML III patients [32,33,35,62]. This causes pain and reduced mobility of the patients. Many patients become wheelchair dependent and/or require orthopedic surgical interventions at a young age [33]. This clearly limits the independency and self-care of these patients, and may impair quality of life [39–41]. Fig. 9 provides a schematic overview of the cascade of events induced by intra-lysosomal GAG accumulation.

8. Treatment of hip disease

There are major obstacles in the successful treatment of hip disease in MPS and ML patients. Factors that complicate treatment are: 1) fetal developmental origin of hip pathology, with abnormal cartilage and bone architecture already present at birth 2) the primary pathology (GAG accumulation) in cartilage and bone that evokes a sequence of events and multiple secondary complications like inflammation, 3) the relative inaccessibility of cartilage and bones for medication due to poor vascularization, 4) the slow cell turnover in cartilage and bone due to poor vascularization, and 5) the fact that not only the hip is affected but that structural abnormalities encompass the entire skeletal system.

The main focus of treatment for hip disease in MPS and ML must be to prevent structural alterations of cartilage and bones as much as possible in early post-natal life, thereby preventing the cascades which evoke the multiple secondary complications. Interventions could be aimed at preventing GAG accumulation, preventing inflammation, or changing hip bone morphology by surgical procedures at an early age.

The next section describes the treatments that are currently available for MPS and ML patients to ameliorate hip disease. Thereafter future
9. Effects of the currently existing disease modifying therapies on the bone in MPS and ML

9.1. Enzyme replacement therapies

Currently enzyme replacement therapy (ERT), in which the deficient enzyme is given to the patients with weekly intravenous infusions, is available for MPS I, II, IV VI and VII. ERT may have some positive effect on bone and/or joint problems, as suggested by studies comparing sibling differing in age at start of ERT, with better outcome on some parameters in the early treated patients \[78–80\]. However, it has become clear that ERT cannot fully prevent the development of skeletal complications. It is questioned if the ERT reaches the lysosomes in bone and cartilage, as vascularization of cartilage and bones is poor \[78–80\]. Disease modifying therapy for the different forms of mucolipidoses is not available. Given the multiple functional lysosomal enzyme deficiencies, ERT with lysosomal enzymes is not an option for these disorders.

9.2. Other disease modifying therapies

Bone-marrow transplantation (BMT) and more recently, hematopoietic stem-cell transplantation (HSCT) therapy are established treatment modalities for young (ideally before 18 months of age) MPS I patients (severest form) \[81\]. This therapy results in significant improvement in cognitive development. However, cartilage and bone problems still develop in HSCT treated MPS I patients \[27,28\]. Skeletal problems such as kyphosis, scoliosis, genu valgum and hip disease may occur and many patients still require orthopedic surgeries later in life \[28,81–85\].

9.3. Surgical procedures

Hip containment surgeries are frequently performed in MPS patients (with exception of the MPS III patients). In MPS I that underwent HSCT at an early age and in MPS IV patients (similar hip disease development to MPS I), the surgical procedures of the hip include pelvic and femoral osteotomy. Both procedures are preferably performed at a young age (often during a single procedure) to widen the dysplastic acetabula and to correct the abnormal femoral neck angle, which is necessary to improve normal pressure of the femoral head on the acetabulum. Over time osteoarthritis cannot be prevented in these patients and total hip replacement is often necessary at young adult age \[30,51,86–92\]. Beside the fact that long term data are missing the improved hip anatomy as a result of containment surgery might improve outcome of hip replacement later in life. In infants with MPS VI it is often difficult to decide which surgical procedure should be performed and at what age, as shape and angle of the femoral heads differ substantially between patients. In these patients another option is to wait until the patient develops severe symptoms of hip disease and then perform either femoral or peri-acetabular osteotomy or total hip replacement \[33\].

In ML III adult patients, varus derotational osteotomy alone was shown not to be sufficient to prevent progression of hip disease, and in all of the patients subjected to this procedure total hip replacement was eventually required \[35\].
It should be noted that surgical interventions (e.g., femoral osteotomy or correction of the angle of the femoral neck) will also change weight bearing abilities in other joints (knees, ankles, or spinal cord) by altering the alignment of these joints. This may also negatively affect shape and function of the other joints than the hip. Vice versa deformity of knees and ankles, which are common in all MPSes may have a negative impact on the outcome of containment surgery of the hips. Therefore, each surgical intervention should be carefully considered, taking the whole weight bearing system into account.

10. Future therapeutic perspectives

In this section possible future therapies will be discussed.

10.1. Enzyme replacement therapy

The effect of ERT on skeletal disease can potentially be improved by binding the recombinant enzyme to specific bone or cartilage-targeting molecules. An example of such an approach, that is currently already used in clinical practice, is the bone targeting ERT used in the treatment of hypophosphatasia, asfotase alfa. Asfotase alfa consists of a recombinant fusion protein comprising the tissue-nonspecific isozyme of alkaline phosphatase (TNSALP) ectodomain, the constant region of the human IgG1 Fc domain, and a terminal deca-aspartate motif for bone targeting. This treatment has shown promising results on skeletal manifestations in this disorder [93].

10.2. Pharmacological therapies targeting bone disease in MPS and ML

Given the import role of inflammation in the etiology of bone disease in MPS and ML, anti-inflammatory drugs may be an alternative option for the treatment of the skeletal symptoms of patients with MPS and ML.

There is some evidence for a beneficial effect of the treatment with immunomodulatory drugs which aim to reduce inflammation in MPS. They do not directly target the underlying disease and will not influence the malformation of the bones. However, they are likely able to reduce the occurrence of secondary osteoarthritis and subsequent cartilage damage in the joints. This, in turn, could reduce pain and preserve mobility to some extent. For example, the drug pentosan polysulfate (PPS), a heparin analog which shows similarities with the molecular structure of heparan sulfate and has potent anti-inflammatory effects, has been reported to reduce cartilage inflammation in patients with arthritis [94] but also in MPS VI rats and MPS I dogs [95,96]. PPS also has pro-chondrogenic properties [97,98]. PPS effectiveness has been studied in a small number of MPS I patients (PPS) [99], suggesting a positive effect on pain and range of motion of the joints, though larger studies of longer duration are needed to confirm this. Furthermore, one of the TNFa inhibitors, Infliximab, reduced joint inflammation in a MPS VI rat model and in a MPS VII mouse model, but its effectiveness has not yet been studied in human patients with MPS or ML [77]. In summary, a beneficial effect of anti-inflammatory drugs on hip disease in MPS has not been studied sufficiently in both preclinical and clinical studies.

Another therapy for MPS and ML could be reducing the formation of GAGs. An ongoing phase 3 trial is currently conducted in adult MPS VI patients with 4-methyl-7-(5-thio-beta-D-xylpyranosyloxy)-2H-chromen-2-one (Odiparcil), a small molecule (b-D-thioxyloside antithrombotic compound [100,101]). This molecule binds to the GAGs dermatan and chondroitin sulfate which promotes the production of a soluble product which can be excreted via the urine, thereby decreasing GAG accumulation in different tissues. In a MPS VI mouse model GAG accumulation in cartilage could be reduced with Odiparcil.

10.3. Other therapies targeting bone disease in MPS and ML

Gene therapies (both AAV gene therapy targeted at the liver and lenti-viral gene therapy via hematopoietic stem cells) aimed at overexpression of the missing enzyme are currently being developed for several types of MPS [102–104].

Gene therapy aiming at overproduction of one particular enzyme is not likely to be effective in ML as the deficient enzyme in ML, GlcNAc-PTase, is a transmembrane protein residing in the Golgi apparatus resulting in the intra-lysosomal deficiency of many different lysosomal enzymes.

10.4. Surgical interventions

Early orthopedic surgeries are essential in MPS and ML patients to correct the anatomical abnormalities of the pelvic and femoral bones. The common orthopedic interventions used to correct dysplastic acetabula, such as Pemberton or Salter osteotomy, may not be efficient in MPS patients. These procedures aim to correct the steepness of the acetabulum, but this is not yet present in MPS and ML patients at an early age. Other procedures such as enlarging the acetabular roof more specifically target the structural alterations observed in MPS and ML. Another possibility is the Shelf procedure (Fig. 10) in which a bone graft is placed just above the hip joint creating a wider acetabular roof (shelf) over the femoral head, enlarging the volume of the acetabulum. This procedure prevents migration of the femoral head and enlarges the weight bearing surface, aimed at preventing the secondary deformation of the femoral head. Ideally, this should be done very early in life in MPS or ML patients, before the slope of the acetabulum changes and alters the femoral head and neck. If performed later in life, when the femoral head is already deformed, the angle of the femoral head has to be corrected, in addition to the Shelf procedure. This combined procedure has been performed in MPS IVA patients and prevented the recurrence of hip subluxation in these patients [105]. However the number of cases published is small and long term follow up is missing.

10.5. Combination of therapies

ERT, HSCT and gene therapy have the potential to achieve systemic (supra)physiological enzyme levels. Even so, as hip disease is already present at birth and the relative inaccessibility of bone and cartilage, it is
doubtful if bone and cartilage disease can be treated effectively in this manner. Therefore, it is likely that combining therapies (e.g., the combination of ERT or gene therapy with an anti-inflammatory treatment or, for MPS I patients, the combination of HSCl with anti-inflammatory treatment) may be another good way forward. Possibly in combination with hip reconstruction surgeries performed early in life.

11. Conclusion

The hip is frequently and severely affected in MPS and ML patients. Hip pathology results in limitations in mobility and pain, which may affect the quality of life. Multiple intra- and extra-articular processes are activated and altered by intra-lysosomal GAG accumulation in chondrocytes, bone cells and in the extracellular matrix. The early start of hip disease, likely already during fetal development, has a lifelong consequences on body structure and function.

The abnormal development of cartilage and bones from very young age in MPS and ML patients forms a challenge when it comes to treatment. Moreover, currently available therapies such as ERT and HSCT, do not significantly improve hip disease, due to preexisting irreversible changes and the low vascularization of cartilage. The focus of future therapies has to be on early intervention, better penetration of cartilage and bone and on prevention of the secondary complications induced by the intra-lysosomal GAG storage. Probably combination of treatments is necessary to achieve optimal results.

Guarantor of the work

Dr. E. Oussoren is the guarantor of this work.

Ethics approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the review.

Submission declaration and verification

The work described has not been published previously (except in the form of a published academic thesis, the chapters described in this review were not published online). It is not under consideration for publication elsewhere. The publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out. If accepted it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Esmee Oussoren; Conceptualization; Data curation; Investigation; Roles/Writing – original draft. Margreet A.E.M. Wagenmakers; Conceptualization; Supervision; Roles/Writing – original draft; Writing – review & editing. Bianca Link; Conceptualization; Writing – review & editing. Jan C. van der Meijden; Visualization; Writing – review & editing. W.W.M. Pim Pijnappel; Writing – review & editing. George J.G. Ruiter; Conceptualization; Supervision; Writing – review & editing. Mirjam Langeveld; Conceptualization; Supervision; Roles/Writing – original draft; Writing – review & editing. Ans T. van der Ploeg; Conceptualization; Supervision; Roles/Writing – original draft; Roles/Writing – review & editing.

Declaration of competing interest

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