Sanfilippo disease (mucopolysaccharidosis type III): Early diagnosis and treatment
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HIGH PREVALENCE OF FEMORAL HEAD NECROSIS IN MUCOPOLYSACCHARIDOSIS TYPE III (SANFILIPPO DISEASE): A NATIONAL, OBSERVATIONAL, CROSS-SECTIONAL STUDY

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ABSTRACT

Background Sanfilippo disease, or Mucopolysaccharidosis type III (MPS III), is a lysosomal storage disorder and a member of the mucopolysaccharidoses (MPSs). MPS III is clinically characterized by progressive neurodegeneration. Skeletal disease is not felt to be an important clinical component in MPS III patients, unlike in the other MPSs.

We conducted radiographic studies in a relatively large group of MPS III patients and detected a high prevalence of osteonecrosis of the femoral head (ONFH).

Methods Thirty-three patients were included in the study. All the patients underwent an X-ray of the pelvis (anteroposterior view). All the X-rays were evaluated by a single, blinded radiologist using a modified Ficat classification system for ONFH (the stages ranged from 0 to IV, with increasing stages signifying more severe abnormalities). Clinical symptoms possibly related to hip disease were recorded. The patients were divided into different phenotypes based on mutational analysis and their plasma heparan sulfate (HS) levels.

Results In 21 of the 33 patients, the disease severity could be predicted by genotype. In 11 of the 12 remaining patients, the phenotype could be assessed via the plasma HS levels. Eight patients (24%) exhibited signs of ONFH (Ficat stage ≥ I), and 6 (75%) of them had bilateral changes. None of the patients with attenuated MPS III (n = 14) had ONFH. In 6 of the patients with a severe phenotype, hip dysplasia was detected as an additional finding. The 7 patients with Ficat stages ≥ II reported hip pain.

Conclusions Femoral head disease, which resembles ONFH, is common in patients with the severe MPS III phenotype. An evaluation of hip disease should be included in follow-up visits with MPS III patients.
INTRODUCTION

Mucopolysaccharidosis type III (MPS III), or Sanfilippo disease, is a rare autosomal recessive lysosomal storage disease characterized by progressive cognitive and motor dysfunction. MPS III is caused by a deficiency in the enzymatic degradation of the glycosaminoglycan (GAG) heparan sulfate (HS). These patients have a deficiency in heparan N-sulfamidase (NS; EC 3.10.1.1), α-N-acetylglucosaminidase (NAGLU; EC: 3.2.1.50), acetyl-coenzyme A:α-glucosaminide N-acetyltransferase (HGSNAT; E.C. 2.3.1.3) or N-acetylglucosamine-6-sulfatase (GNS; EC 3.1.6.14), dividing them in 4 biochemically different subtypes: types A, B, C and D, respectively (OMIM#'s 252900, 252920, 252930, and 252940).

The birth prevalence of MPS III is estimated to be 0.28-4.1 per 100,000 newborns. The clinical signs, symptoms and disease development in the different MPS III subtypes are indistinguishable. In all patients, an initial, symptom-free interval with normal development is followed by developmental slowing and arrest, and a progressive cognitive decline follows. Behavioral problems including severe hyperactivity, aggressive and/or anxious behavior and sleep problems usually begin around the onset of cognitive decline. Other common symptoms are recurrent ear, nose and throat infections, episodes of diarrhea and hepatomegaly. Patients often have mild facial dysmorphisms.

The somatic signs and symptoms of MPS III are relatively mild compared to those observed in the other mucopolysaccharidoses (MPSs). In the other MPSs, which are caused by the deficient degradation of other GAGs (dermatan and heparan sulfate in MPS I and II; keratan sulfate in MPS IV; dermatan sulfate in MPS VI; and dermatan, heparan and chondroitin sulfate in MPS VII), skeletal disease is one of the most prominent symptoms. Abnormal skeletal remodeling and endochondral and intramembranous ossification lead to a group of multiple radiographic skeletal changes termed ‘dysostosis multiplex’. The causes of skeletal disease in these MPSs have not yet been fully elucidated, but the accumulation of dermatan and keratan sulfate is regarded as the primary cause, producing inflammation with the destruction of the bone and cartilage and disturbances in the integrity of the growth plates.

Hip dysplasia is part of the dysostosis multiplex in MPS I and VI and, to a lesser extent, in MPS II and IV. In addition, proximal femoral epiphyseal dysplasia with the flattening of the femoral head followed by progressive destruction is frequently reported in MPS IV and VI, consistent with the hypothesis that the accumulation of dermatan and keratan sulfate is the primary cause of the pathophysiology of skeletal disease in the MPSs. Skeletal disease was not considered to have a significant impact in MPS III, until White et al. (2011) examined 18 MPS III patients for skeletal manifestations and detected hip pathology in 10 patients, with dysplasia in 8 and signs of osteonecrosis of the femoral head (ONFH) in 4.

Here, we studied the prevalence of ONFH and hip dysplasia in a radiographic cross-sectional study of 33 patients with MPS III; we found signs of ONFH in 8 patients (24%) and dysplasia in 6 (18%). Because patients with MPS III are generally unable to reliably report and/or localize pain due to cognitive impairment, the optimal care of MPS III patients should include assessments of hip pathology during regular follow-up visits.
METHODS

Study population
Participants were recruited between April and August 2012. A total of 46 patients with MPS III who live in the Netherlands are currently under the direct care of our center and were considered for inclusion in this study. Patients who were fully institutionalized due to advanced cognitive impairment (n = 10), were not approached for participation in this study due to potential logistic problems with hospital transfers for X-ray studies. The families of 3 of the remaining 36 patients refused participation because of the potential psychological impact of participation on the child. Therefore, 33 patients were included in the study.

Disease severity
The patients with MPS IIIA and IIIB were divided into 3 phenotypes, severe, intermediate and attenuated, in the presence of a predictive genotype. The disease severity of all the MPS IIIC patients, and of the MPS IIIA and IIIB patients with uninformative genotypes, was assessed based on plasma HS levels. Patients with HS levels > 990 ng/ml were classified as severely affected, whereas patients with HS levels < 990 ng/ml were classified as less severely affected.

Radiographic studies
Anteroposterior (AP) and frog-leg lateral X-ray studies of the hips were performed in one session. If hip X-rays of sufficient quality had been produced during the 12 months prior to the start of the study, they were examined instead.

Ethical approval
This study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam. Written informed consent was obtained for all the study participants.

Radiographic evaluation
All the X-rays were evaluated by a single, experienced radiologist who was blinded to the patients’ clinical condition. An adapted version of the modified classification system of Ficat and Arlet, which was designed for the classification of ONFH, was used to quantify the radiographic changes. The modified Ficat scoring system consisted of 6 stages, with stage 0 characterized by the absence of radiographic findings. In stage I, the changes observed on radiographic studies are either absent or mild; stages IIA, IIB, III and IV indicate radiographic changes of increasing severity. Because the Ficat system was designed for patients who have osteonecrosis or are expected to develop it, we modified the classifications as follows: the patient was scored as stage 0 if there were no radiological signs of ONFH, and stage I was scored if there were mild radiological changes, independent of clinical signs (Table 1).

Acetabular dysplasia was indicated by a lateral center-edge angle of less than 20° on an AP pelvic radiograph.
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Questionnaire for clinical symptoms
We utilized a brief questionnaire to collect information about the potential clinical signs and symptoms of femoral head disease in MPS III patients. The following questions were asked: Do you think that the patient experiences hip pain? (0 = no pain, 1 = very mild pain, 2 = mild pain, 3 = moderate pain and 4 = severe pain). On which side do you think that the pain is located? (0 = no hip pain, 1 = left hip, 2 = right hip and 3 = both hips).

Statistical analysis
Differences between the groups (ONFH and no ONFH) were assessed with an independent t-test for the normally distributed continuous variable of patient age and with Fisher’s exact test for categorical variables. Statistical analyses were performed using SPSS, version 19.0. A p-value < 0.05 was considered significant.

RESULTS

Patients
Thirty-three patients were included in the study. Sixteen of the patients had MPS subtype IIIA, 9 had MPS IIIB, and 8 had MPS IIIC. Nineteen of the 33 patients (57.6%) were male.

Assessment of phenotype
In 21 of the 25 patients with MPS III type A or B, the disease severity could be predicted by genotype.\(^\text{13,14}\) Of the 12 patients (4 with type A or B and 8 with type C) who lacked a predictive genotype, 11 were classified on the basis of the plasma level of HS.\(^\text{15}\) Eight of these patients were classified as severe, and 3 were classified as less severe. A phenotypic prediction was impossible for one (MPS IIIC) patient because no blood sample was available.

Radiography
All 33 patients underwent plain radiography of the hips with an AP view. Frog-leg lateral view radiographs were also obtained for 30 (91%) but were impossible in 3 patients due to severe hyperactivity. Signs of ONFH (Ficat stage ≥ I, Table 2) were detected in 8 patients (24%). Six patients had bilateral ONFH, and 2 had unilateral ONFH. The Ficat stages of the 14 affected hips were classified as follows: stage I, 2 hips; stage IIA, 1 hip; stage IIB, 2 hips; 6

<table>
<thead>
<tr>
<th>Ficat stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Normal radiograph</td>
</tr>
<tr>
<td>Stage I</td>
<td>Minor changes on plain radiograph</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Sclerosis or cysts of femoral head, diffuse porosis</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Crescentic subchondral line, flattening of the femoral head</td>
</tr>
<tr>
<td>Stage III</td>
<td>Broken contour of the head, normal joint space</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Collapse, flattened contour of the femoral head, decreased joint space, osteoarthritis</td>
</tr>
</tbody>
</table>

Table 1. The modification of the modified Ficat classification used in this study.
stage III, 5 hips; and stage IV, 4 hips. ONFH was more prevalent among the patients with the severe phenotype (Figure 2). In 7 of the 15 patients with the severe phenotype, signs of ONFH were detected. No differences in the presence of ONFH were observed between the sexes (Table 2). Figure 1 shows the progression of ONFH on the X-rays of one MPS IIIC patient over a period of 4 years.

The mean age of the patients with ONFH tended to be lower than that of the patients without ONFH, although this difference was not statistically significant (Table 2). Seven patients with Ficat stages ≥ II were between 10 and 17 years of age.

Table 2. Differences between the groups with and without ONFH.

<table>
<thead>
<tr>
<th></th>
<th>Patients with ONFH (n = 8)</th>
<th>Patients without ONFH (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (75)</td>
<td>13 (52)</td>
<td>0.42</td>
</tr>
<tr>
<td>Female</td>
<td>2 (25)</td>
<td>12 (48)</td>
<td></td>
</tr>
<tr>
<td>Hip pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain reported</td>
<td>7 (87)</td>
<td>8 (32)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years (mean, range)</td>
<td>12.4 (3-17)</td>
<td>16.6 (5-33)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

The numbers indicate the number of patients per group, with the percentage of the total given between brackets.

Other skeletal changes on radiography

Five patients had unilateral dysplasia, and one had bilateral dysplasia. All the patients with dysplasia exhibited a severe phenotype. Four of these 6 patients (66%) also had ONFH.

Several other abnormalities were detected with radiography. In 8 patients, abnormal contours of the pubic bones were observed. In these patients, the outer ends of the pubic bones (where the symphysis pubis is formed) were shaped irregularly. Cystic lesions in locations other than the femoral head were noted in 4 patients; these included the acetabular roof, the pubic bone and the sacroiliac joint. The acetabulum had an immature or ragged aspect in 8 patients, and the iliac side of the sacroiliac joint had a ragged aspect in one patient. One patient exhibited prominently rounded iliac wings with mild inferior tapering of the ilea, and another patient had a dislocated hip. Six patients exhibited hip dysplasia.

Clinical symptoms and ONFH

For 15 of the 33 patients, the parents or caregivers indicated that the patient might have pain in one or both hips. Seven of these 15 patients had significant ONFH (Ficat stage ≥ II). One patient with an abnormal Ficat score (stage I) exhibited no clinical symptoms of ONFH. In 8 patients for whom the parents or caregivers indicated hip pain, no abnormalities were detected with radiography. Two patients with severe hip pain, both Ficat stage IV, later underwent surgery (the removal of the femoral head or a girdle-stone procedure; Figure 1).
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Figure 1. Pelvic X-ray of one patient with MPS IIIC. A. X-ray at age 13.9 years: Ficat stage III on the right and left sides (lucencies and interruptions of the femoral heads). B. X-ray at age 17.0 years: Ficat stage IV on the right and left sides (increased subchondral cystic abnormalities in the femoral heads and decreased joint spaces on both sides). C. X-ray from 2012 after surgery at age 17.9 years: right femoral head removed, Ficat stage IV on the left side.
DISCUSSION

In this study, we showed that femoral head disease is common among patients with MPS III. The observed changes in the femoral head closely resembled those reported in young patients with ONFH (head avascular necrosis or Legg-Calvé-Perthes (LCP) syndrome). We demonstrated that a minor modification of the modified Ficat classification could be used to distinguish the different stages of progressive femoral head pathology in MPS III. The prevalence of ONFH in our cross-sectional study (24%) is highly similar to the prevalence (22%) reported in the only other (smaller) study on this subject. In addition, we found several other changes in the hip and pelvic bones, demonstrating that patients with MPS III have a more general skeletal disease (not limited to ONFH), which is in accordance with previous reports of deformities of the spinal column and extremities in MPS III patients. There is some overlap between patients with hip dysplasia and those with ONFH; hip dysplasia may therefore be a risk factor for developing ONFH. However, not all the patients with ONFH had hip dysplasia, and the hip dysplasia was unilateral in almost all our patients, whereas the ONFH was often bilateral.

Because none of the patients with the attenuated MPS III phenotype showed signs of ONFH, disease severity appears to be a risk factor for ONFH in MPS III patients. There was no significant difference in age between the patients with and without ONFH (Table 2). However, all the patients with severe ONFH (Ficat stage III-IV) had already reached adolescence.

The primary cause of the dysostosis multiplex in MPS I, II and VI is generally considered to be the accumulation of dermatan sulfate; in MPS IV, the accumulation of keratan sulfate is considered responsible. Our findings regarding femoral head disease in MPS III patients suggest that the accumulation of HS alone may also lead to bone disease, although to a lesser extent than the accumulation of the other GAGs. Another source of the dysostosis
multiplex in MPS III might be the secondary intracellular accumulation of smaller quantities of dermatan sulfate, as has been demonstrated in MPS III fibroblasts. The general pathogenesis of GAG-induced skeletal disease is complex; it involves osteoclast dysfunction mediated by the inhibition of the collagenase activity of cathepsin K by the accumulation of GAGs, reductions in chondrocyte proliferation and inflammatory changes in the growth plates. The identification of the precise roles of these mechanisms in bone disease in MPSs may lead to targeted therapeutic approaches. As future therapies will probably target mainly CNS disease, and have the potential to increase the lifespan of patients, skeletal disease will likely to become a more prominent feature in MPS III patients. Therefore this study might have implications for the design of the currently and future treatment studies in MPS III patients. The radiographic changes that indicate the presence of ONFH as part of the dysostosis multiplex are most commonly observed in MPS III, IV and VI. White et al. have suggested that epiphyseal dysplasia causes these radiological changes and resembles LCP or idiopathic femoral head osteonecrosis in childhood. The femoral head abnormalities seen in MPSs, which we reported as ONFH here, differ from LCP in several aspects. LCP is usually unilateral, whereas ONFH in MPSs is generally bilateral. Indeed, we observed bilateral ONFH in 6 of the 8 cases with ONFH. Moreover, LCP is a self-limiting disease that involves bone remodeling in its final stage, whereas MPS-related ONFH is not associated with healing or the progression of femoral head abnormalities over time. The progression over time of ONFH in an MPS III patient, without any signs of healing, is shown in Figure 1. Finally, most cystic lesions in LCP occur in the metaphysis, whereas the cystic lesions in MPSs are present in the epiphysis and the acetabulum, as reported in the present series of MPS III patients.

MPS III patients with ONFH may experience severe hip pain, necessitating chronic pain medication. Hip disease in MPS III may necessitate surgery if the pain medication is insufficient. Two patients in our series, both of whom had a Ficat stage of IV in both hips and were non-ambulant at the time of surgery due to advanced central nervous system disease, underwent a unilateral removal of the femoral head on the most painful side. Both patients were pain free on the operated side after surgery, and their quality of life had significantly improved. Because of the possible psychological impact of surgery on MPS III patients and their possible difficulties during rehabilitation, surgery should be considered carefully and might best be reserved for MPS III patients with incapacitating hip pain who demonstrate an insufficient response to pain medication. Furthermore, future management with anti-inflammatory medicines such as pentosan polysulfate (PPS) might provide significant clinical benefits in treating ONFH.

This study has several potential limitations. First, patients who were fully institutionalized were not included. Because these patients probably have more advanced forms of disease, our observation that ONFH occurs in approximately 25% of MPS III patients may underestimate its true prevalence. Second, the parents of significant numbers of patients with no signs of ONFH on radiography reported hip pain in their children. Patient pain or discomfort caused by factors other than ONFH may have been
erroneously attributed to hip pain because the parents were aware of the focus of the study, which may have prompted the attribution of discomfort or pain to hip disease.

CONCLUSIONS
Because pain may be difficult to assess and localize in MPS III patients with advanced cognitive decline and behavioral disturbances, radiographic studies of the hips may detect pathology in MPS III patients with otherwise unexplained signs of discomfort or pain. We recommend that these studies be conducted at regular intervals (e.g., yearly) during follow-up from the age of 10 years onward, at least for patients with intermediate or severe phenotypes. Moreover, this study shows that dysostosis multiplex is a part of MPS III disease, and therefore further skeletal involvement should be studied in MPS III patients.
REFERENCES