# OPHTHALMOLOGICAL FINDINGS IN A PATIENT WITH MUCOLIPIDOSIS III (PSEUDO- HURLER POLYDYSTROPHY). A CASE REPORT.

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## SUMMARY:

Mucolipidosis III (Pseudo- Hurler Polydystrophy) is a rare autosomal recessively inherited Hurler-like disease. The ophthalmological findings in these patients include a triad of mild retinopathy, corneal clouding and hyperopic astigmatism. We present a patient with these ophthalmological characteristics.

## RÉSUMÉ:

La Mucolipidose III (Pseudo- Hurler Polydystrophie) est une maladie héréditaire autosomale récessive très rare. Les caractéristiques ophtalmologiques de cette maladie consistent en la triade de rétinopathie légère, opacités de la cornée et astigmatisme hyperopique. Une patiente avec des symptômes ophtalmologiques typiques est présentée.

## SAMENVATTING:

Mucolipidosis III ( Pseudo- Hurler Polydystrophy) is een zeldzame autosomaal recessief erfelijke aandoening. De oftalmologische bevindingen bij deze patiënten omvatten een typische triade van milde retinopathie, corneale opaciteiten en hypermetroop astigmatisme. We stellen een patiëntje voor met de bovenbenoemde oftalmologische afwijkingen.

## KEY-WORDS:

Pseudo- Hurler polydystrophy, corneal clouding, retinopathy.

## MOTS-CLÉS:

Pseudo- Hurler polydystrophie, opacités de la cornée, rétinopathie.

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## INTRODUCTION

Mucolipidosis II (I-cell disease, Leroy disease) and III (ML-III or pseudo-Hurler polydystrophy) are respectively the severe and mild forms of an autosomal recessive genetic disorder characterized by deficient activity of the enzyme UDP-N-acetylglucosamine:lysosomal enzyme N-acetylglucosaminyl-1-phosphotransferase (termed phosphotransferase). This enzyme provides the first step in the biosynthesis of the mannose-6-phosphate lysosome-targeting marker on nascent lysosomal enzymes. Its deficiency results in defective posttranslational processing and transport of lysosomal enzymes, leading to deficient activity of multiple enzymes in the lysosomes, but increased activity of these enzymes in the extracellular environment (2, 3, 5).

Patients with mucolipidosis II present a severe storage phenotype in the perinatal period. In contrast, patients with the less severe phenotype of mucolipidosis III, or pseudo-Hurler polydystrophy, present at the ages of 2 to 4 years with stiffness of the hand joints, progressively restricted joint mobility, short stature, and severely dysplastic hip joints. They develop a Hurler-like dysmorphism of the face and dysostosis multiplex of the skeleton, resembling Hurler syndrome. Other common symptoms include cardiac valvular involvement (especially aortic insufficiency), restrictive pulmonary disease, gingival hyperplasia and carpal tunnel syndrome. Some have learning disabilities or mild mental retardation. Affected children have normal puberty, and survival into early adulthood is common. In contrast to other mucopolysaccharidoses, such as Hurler syndrome, mucopolysaccharide excretion in the urine is not increased. The biochemical diagnosis is made by the demonstration of deficient intracellular activities of some lysosomal enzymes and increased activities in serum (2, 3, 5).

The triad of corneal clouding, mild retinopathy and hyperopic astigmatism is a consistent ophthalmological finding in patients with ML-III (7). In this study we report the eye findings in a patient with ML-III and contrast these with the corneal findings in Hurler and Hurler-Scheie syndrome. Hurler syndrome and its milder variant Hurler-Scheie syndrome, which clinically resemble ML-III, are diseases caused by a deficiency of a single lysosomal enzyme, α-L-iduronidase,

## CASE REPORT

A thirteen-year-old girl with the clinical characteristics of ML-III presented for ophthalmological evaluation as a part of a multidisciplinary investigation. She was the first child born to unrelated and healthy parents after a normal pregnancy and delivery. Retardation of psychomotor development was noted during the second year when she started to walk at the age of 20 months, but verbal skills were normal for her age. Striking hip dysplasia in a developing spondylometaphyseal skeletal dysplasia was noted in addition to facial coarseness, short neck, short and pronounced pectus and restricted joint mobility in the knees and hips. At the age of ten she developed a hypertrophic cardiomyopathy with aortic and mitral valvular insufficiency resulting in pulmonary distress and dyspnoea. Hearing loss due to otitis serosa was marked at the age of eleven. At 13 years, the kyphosis was exaggerated by spontaneous vertebral fracture. Pronounced cardiopathy and restrictive dyspnoea in addition to skeletal dysplasia limited her mobility, making her wheelchair-bound. She weighed 16.8 kg and measured 103.5 cm (<<P3); her head circumference was 51.9 cm (P10- P25). There were signs of hand musculature atrophy and electromyographic studies confirmed bilateral carpal tunnel syndrome. She was treated with beta-blockers, lisinopril and furosemide.

The biochemical diagnosis was suggested by a strikingly elevated arylsulfatase A activity in the serum: 9165 mU/l (control 126-540). Fibroblasts showed deficient intracellular activity of N-acetyl-β-D-glucosaminidase A: 113 nmol/mg/hour (control 950-1750) and of total (A and B) N-acetyl-β-D-glucosaminidase: 1193 nmol/mg/hour (control 6000-20000), in contrast to normal activity of β-glucosidase, which has mannose-6-phosphate-independent lysosomal targeting. A deficient activity of the N-acetylglucosaminylphosphotransferase of 3 pmol/mg/hour (control 40-90) completed the diagnostic studies.

Ophthalmological examination at the age of 12 showed normal pupils and reflexes. Visual acuity was 1.0 (Sn 1) in both eyes with a hypermetropic correction of +2 (+0.5 / 90°) for the right eye and +3 (+0.5 / 90°) for the left eye. The axial length was 20 mm and 20.1 mm in

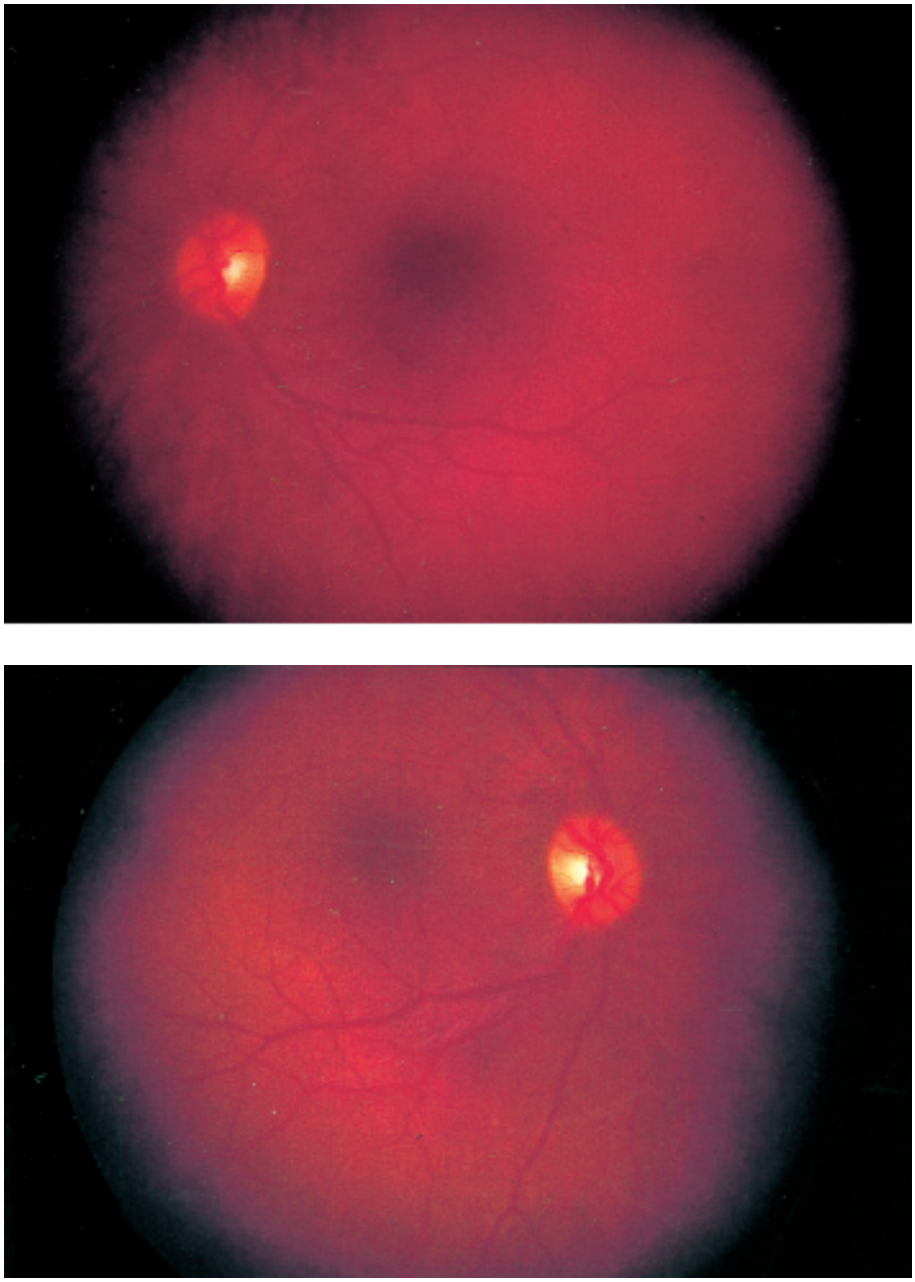

*Fig 1 and 2.* Fundus photographs right and left. Note the mild macular surface wrinkling as horizontal lines, especially at the nasal and temporal side of the fovea.

the right and left eyes respectively. There were no signs of squint and the ocular motility was not restricted. The visual field examination using Goldmann perimetry showed normal sectoral limits. On funduscopy normal optic nerves, mild retinal vascular tortuosity, and mild macular surface wrinkling (Fig. 1, 2) were visualized.

Corneal clouding was evident on biomicroscopic examination (Fig. 3). The opacities were

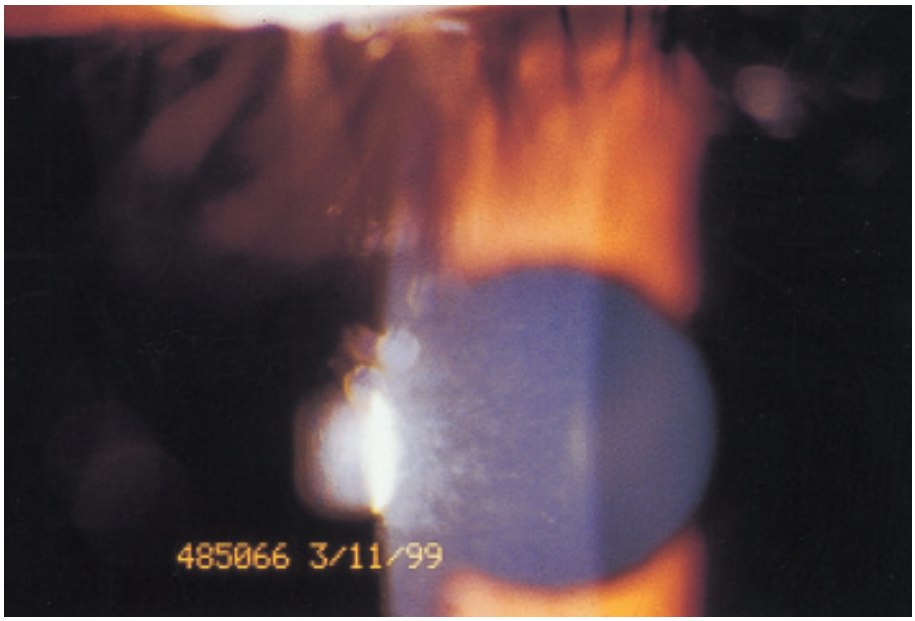


*Fig 3.* Showing the discrete corneal clouding as fine pinpoint opacities.

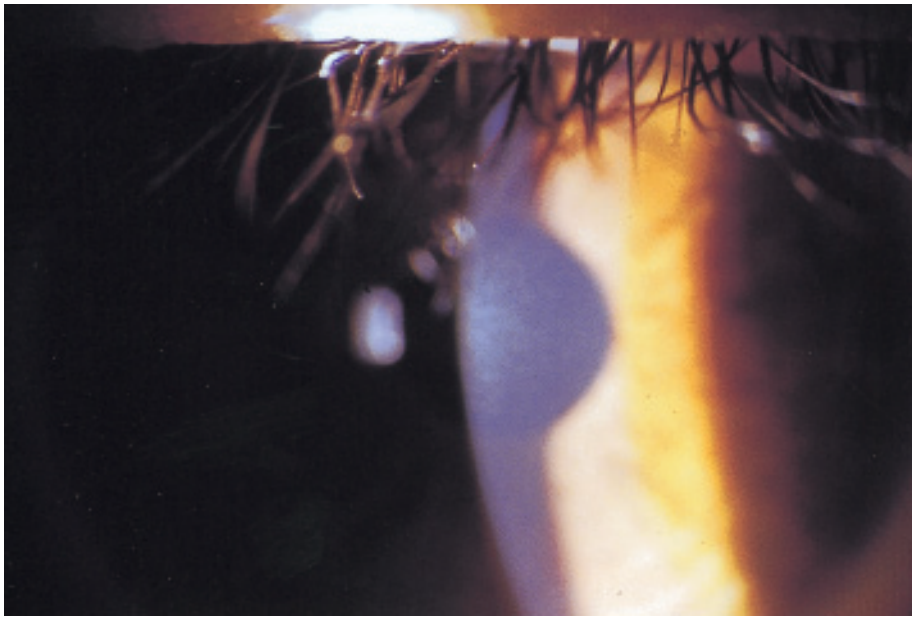

*Fig 4.* Corneal clouding. Fine opacities involve the full corneal thickness, except for the epithelium.

fine and discrete, pinpoint dots-like, and involved the full corneal thickness (Fig. 4) except for the epithelium. The corneal clouding was markedly more severe in an age-matched patient with Hurler-Scheie syndrome. The corneas are markedly cloudy and the fundi can no longer be visualized.

## DISCUSSION

Our patient exhibited the typical clinical and enzymatic findings of mucolipidosis III. The triad of corneal clouding, mild retinopathy and hyperopic astigmatism is a consistent ophthalmological finding in ML-III (7).

Corneal clouding in ML-III is initially mild. It increases with age, progressing to full-thickness involvement. It usually does not affect vision. The histopathology of the cornea has not yet been described in this condition. Electron microscopical examination of a conjunctival biopsy showed an abnormal accumulation of acid mucopolysaccharides in fibroblasts in an arranged membranous lamellar manner (6). Extrapolating from the similarity between conjunctival connective tissue and cornea, the mechanism of corneal clouding in these patients has been attributed to an abnormal accumulation of storage material in and around stromal keratocytes in the anterior and posterior stroma (6). The epithelial cells are not involved. Therefore the interface between the cornea and tear film is regular, and good visual acuity preserved. A penetrating keratoplasty would be a good alternative for the patients with a disturbing corneal clouding.

Corneal clouding is also seen in mucopolysaccharidoses caused by deficiencies in a single lysosomal enzyme, such as Hurler syndrome (MPS-I), Morquio syndrome (MPS-IV), Maroteaux-Lamy syndrome (MPS-VI), and variably in Sly syndrome (MPS-VII). In contrast corneal clouding is absent in Hunter syndrome (MPS-II) and Sanfilippo syndrome (MPS-III). Patients with ML-III clinically resemble patients with Hurler-Scheie syndrome. The corneal clouding in these patients is more severe and early in presentation, and in some severe cases neovascularization and chronic corneal ulceration have been reported (4).

Optic nerve head swelling of various degree can occur in ML-III and, if severe, can be associated with progressive loss of visual acuity. There are different hypotheses on the pathogenesis of the optic nerve head swelling (7). The posterior sclera is thickened because of the abnormal storage of acid mucopolysaccharides, therefore the pressure increases within the optic nerve sheath and hinders the axoplasmic reflux. Hyperopia may also explain the apparent pseudopapiloedema. The origin of surface wrinkling maculopathy and retinal vascular retinopathy is unknown.It may reflect underlying retinal damage secondary to the abnormal storage process and the formation of epiretinal membranes. The vision could be affected with progressive retinopathy. Our patient showed mild retinal changes. In contrast to other lysosomal storage disorders, such as Hurler syndrome, vision in ML III remains largely unaffected. ERG wasn't performed in our patient because of the absence of any visual problems, and when performed in previously published patients showed consistently a normal response in ML-III patients (1, 4). In the presence of pronounced corneal clouding an electroretinogram is a useful adjunct in the evaluation of ML-III patients with regard to their postoperative prognosis for keratoplasty.

## CONCLUSION

In consistency with previous reports, our patient shows the characteristic triad of mild corneal clouding, mild retinopathy and hyperopic astigmatism. Hyperopia and astigmatism are mild; the macular wrinkling is discrete. Corneal clouding does not affect the visual acuity and there are no signs of papiloedema. These findings are consistent with other observations (7) on the slow progression of the ophthalmological symptoms in patients with ML-III. The ophthalmological findings are mild and only very slowly progressing, with preserved good visual acuity with optimal correction. A follow-up examination of our patient in July 2002 showed no progression in ophthalmological findings. This contrasts to the severe corneal involvement in Hurler and Hurler-Scheie syndrome.

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