Pediatr Radiol (2008) 38:543–550
DOI 10.1007/s00247-008-0788-y

ORIGINAL ARTICLE

Sonographic ocular findings in patients with mucopolysaccharidoses I, II and VI

Reinhard G. Schumacher · Rita Brzezinska · Gudrun Schulze-Frenking · Susanne Pitz

Received: 20 June 2007 / Revised: 24 October 2007 / Accepted: 21 December 2007 / Published online: 26 February 2008

Abstract
Background Ophthalmological complications in patients with mucopolysaccharidosis (MPS) are clouding of the cornea, glaucoma, optic neuropathy, and degeneration of the retina. These changes may impair visual function to the point of total loss of vision.
Objective To document the ophthalmological changes demonstrated by grey-scale US in patients with MPS.
Materials and methods A total of 65 patients with MPS (18 type I, 12 type II, 35 type VI) including a subgroup of 30 undergoing enzyme replacement therapy (ERT) were studied by US of the globe and optic nerve.
Results Average scleral thickness at the posterior pole of the globe measured 2.02–2.58 mm (normal range 1.4–1.7 mm), the average diameter of the optic nerve and its sheath measured 5.35–6.71 mm (normal <4.5 mm). All medians were statistically significantly different from those of healthy volunteers. Concomitantly there was hypermetropia of up to 7.5 dioptres. During a mean follow-up of 3.1 years there was no distinct progression in scleral or optic nerve complex thickness.
Conclusion The optic nerve sheath and sclera were clearly thickened in comparison to normal values. Many morphological changes in the eye and optic nerve were already present at the time of the initial clinical diagnosis, and thus seem to develop very early in the course of the disease. ERT in our patients did not seem to alter the US characteristics of the globe or optic nerve.

Keywords Mucopolysaccharidoses · Ultrasonography · Eye · Optic nerve · Children

R. G. Schumacher (✉) · R. Brzezinska
Department of Paediatric Radiology,
University Kinderklinik,
55124 Mainz, Germany
e-mail: schumach@uni-mainz.de

G. Schulze-Frenking
Hospital for Sick Children, University of Mainz,
Mainz, Germany

S. Pitz
Eye Clinic,
University of Mainz,
Mainz, Germany

Introduction

The mucopolysaccharidoses (MPS) are a group of rare inherited metabolic disorders involving the incomplete degradation of complex carbohydrates because of the absence/deficiency of lysosomal enzymes. This results in the intra- and extracellular deposition of acid mucopolysaccharides (glycosaminoglycans, GAG). A total of eight types of MPS with 12 subgroups have been identified. The overall incidence for all types of MPS is approximately 1 in 20,000 live births [1]. The clinical signs of MPS types I, II and VI are, in principle, similar to one another. Nevertheless, the clinical course within the groups varies greatly and life-span may be drastically reduced. The systemic findings are: coarse or rough facial features, typical deformities of the skeleton (dysostosis multiplex), myelomalacia resulting from constriction at the craniocervical junction, communicating hydrocephalus, cardiomyopathy, stiff joints, and hepatosplenomegaly.

Ophthalmological changes in patients of MPS type I are well known in all subtypes. They consist of clouding of the cornea, degeneration of the retina, widening of the optic nerve and/or optic atrophy. Atrophy limits the therapeutic effectiveness of corneal transplantation. In patients with

subtype Scheie, corneal clouding develops that may be less severe and does not always result in a condition that would make transplantation necessary. Retinal dystrophy may occur, but papilloedema rarely develops in this subtype. Patients with subtype Hurler/Scheie show intermediate symptoms [2].

Patients with MPS type II (Hunter) may develop exophthalmus due to shallow orbits. The ocular findings comprise papilloedema, atrophy of the optic nerve and dystrophy of the retina. Clouding of the cornea is mild and usually does not impair visual function [2]. Patients with MPS type VI (Maroteaux-Lamy) develop progressive clouding of the cornea that can make corneal transplantation necessary. Retinal dystrophy has not yet been observed. Papilloedema is due to secondary hydrocephalus that can eventually lead to atrophy of the optic nerve. Glaucoma develops slightly more often than in other groups [2].

We had the opportunity to study the eye and optic nerve by US in three different groups of patients with MPS (types I, II and VI) receiving and not receiving enzyme replacement therapy (ERT). We systematically documented the findings regarding the sclera and optic nerve. We also performed serial evaluations of patients undergoing ERT.

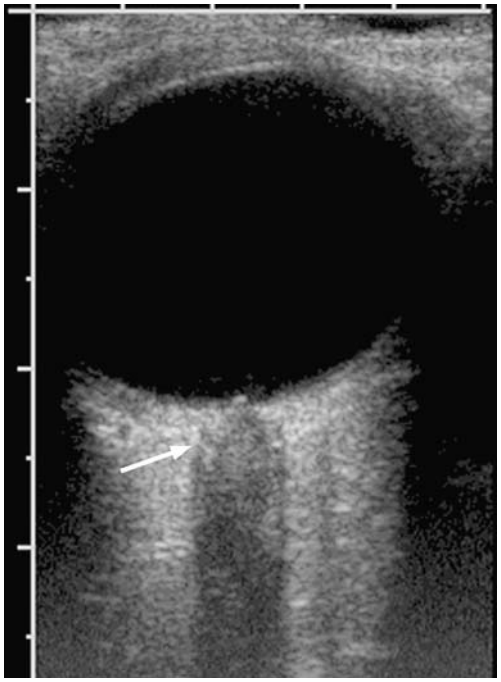

Fig. 1 Normal child. Transbulbar US image shows the vitreous body, optic disc, optic nerve with typical "gothic" origin (*arrow*), arachnoid mater, and retrobulbar fat of high echogenicity

Patients and methods

Patients with MPS were referred from our Centre for Metabolic Diseases. The group with MPS type I consisted exclusively of patients with subtypes Hurler/Scheie and Scheie. A subgroup of these patients with MPS types I, II and VI were included in studies of ERT (detailed inclusion criteria are given in references 3–5) or received ERT after it was approved by the European Medicine Agency. Informed consent was obtained from all patients who participated in the study, or their parents. The protocol was approved in all its parts by the Ethics Committee of the General Medical Council of Rheinland-Pfalz.

We performed transbulbar grey-scale US as described elsewhere [6, 7]. We examined the posterior part of the globe, the optic nerve head and the retrobulbar optic nerve according to recognized standards (Fig. 1). Healthy volunteers were studied to establish normal US values. Two measurements in each eye were taken in each volunteer (Fig. 2).

We used a linear transducer operating at 8–11.5 MHz. The energy was reduced by −10 dB and the mechanical index was limited to 0.14 in order to protect the sensitive neural structures of the eye from mechanical damage. The transverse physical resolution of the transducer (Sequoia 512, transducer 15L8; Siemens, Erlangen, Germany) was 0.2 mm and the axial resolution was 0.19 mm in focus at 13 MHz. The sclera (uveal tract–retina complex, SRC) was measured in the immediate vicinity of the optic disc on the nasal or temporal side. Because US cannot discriminate the individual layers of the outer covering of the globe, we measured the total thickness of all three layers (retina, uveal tract, and sclera). The diameter of the optic nerve sheath (ONS) was determined 3 mm beyond where the nerve passed through the lamina cribrosa.

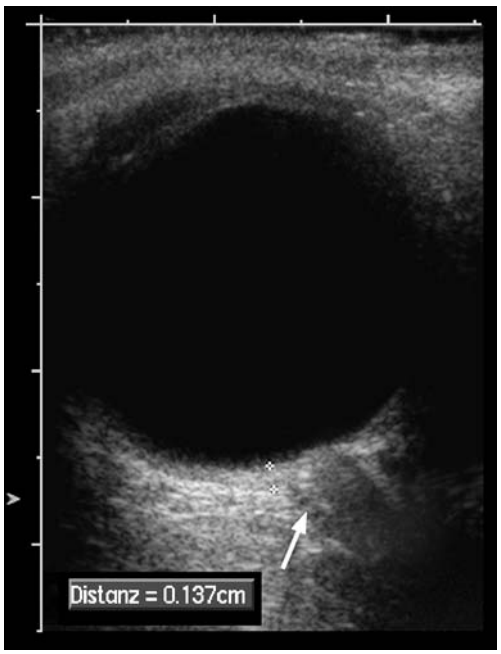

Fig. 2 Normal adult. Transbulbar US image shows the sclera–retina complex adjacent to the optic disc (*callipers*) measuring 1.37 mm and the optic nerve with semicircular origin (*arrow*)

We applied the sonographic standard diameter of the ONS as published [7, 8]. For the standard thickness for the sclera and retina we used histological data from textbooks [9, 10] and compared them with our sonographic normal population. Due to marked differences in variability between the volunteer and MPS groups an independent pooled Student's *t*-test for comparing groups could not be used. We applied the nonparametric Mann-Whitney U-test in spite of the fact that this test is more prone to miss genuine differences. The relationship between patient age and SRC thickness was calculated by regression analysis (least squares fit to the data).

Patients with MPS types II and VI were additionally examined ophthalmologically to document ophthalmological changes. Best corrected visual acuity was tested using Snellen charts. The length of the visual axis was determined by optical interferometry which was followed by slit-lamp examination and fundoscopy. Patients with MPS type I could not be studied ophthalmologically due to organizational problems.

Results

We scanned a total of 65 patients with MPS, including 30 undergoing ERT, and 14 healthy volunteers. Demographic details are given in Table 1. Six patients were siblings. We recorded baseline measurements of SRC thickness and ONS diameter in all 65 patients, and also recorded serial measurements of the SRC in 28 patients (including 24 on ERT), and of the ONS in 36 (Tables 1 and 2). The maximum duration of follow-up was 9 years (mean 3.5 years; details given below).

Patients with MPS type I were the first to receive ERT and consequently in this subgroup of nine patients the duration of ERT was the longest of all groups. The average follow-up in these patients was 1.6 years (range 0–5 years). Patients treated for less than 6 months were excluded from evaluation. Hence, the number of patients in the last column of Table 1 is lower than the total of patients treated because the time of treatment was too short for follow-up studies.

Measurements

SRC

Measurement of SRC thickness is shown in Figs. 2 and 3, and Table 1 shows baseline and serial measurements of SRC thickness. Age dependence of SRC thickness was tested by regression analysis:

MPS type I: $y = 0.047x + 1.484$ ($r = 0.53$)
MPS type II: $y = 0.062x + 1.789$ ($r = 0.09$)
MPS type VI: $y = 0.018x + 2.236$ ($r = 0.26$)

Table 1 Thickness of the SRC in healthy volunteers and patients with MPS

Subjects	No. of subjects		Age (years)		SRC thickness (mm)		Significance levels (baseline measurements)[a]	Mean SRC thicknesses over observation period (mm)[b]			Mean SRC thicknesses in those on ERT		
	Total	ERT	Range	Mean	Mean	Range		First measurement	Last measurement	No. of follow-up studies	First measurement	Last measurement	No. of follow-up studies
Volunteers	14	–	3–52	23.4	1.56	1.4–1.7							
MPS type I	18	9	3–44	18.9	2.02	1.4–2.6	n.s.	2.03	2.1	7	2.03	2.1	7
MPS type II	12	7	2–42	16.4	2.48	1.3–4.0	$P<0.001$	2.2	2.66	6	2.2	2.9	4
MPS type VI	35	14	2–42	13.6	2.58	1.7–4.2	$P<0.001$	2.65	2.6	15	2.7	2.6	13

[a] Mann-Whitney U-test.
[b] Mean observation period 3.5 years (range 1–9 years).

Table 2 Dural ONS diameter in healthy volunteers and patients with MPS

Subjects	No. of subjects	Age (years)		ONS diameter (mm)		Significance levels (baseline measurements)[a]	Mean ONS diameters over observation period (mm)[b]		
		Range	Mean	Mean	Range		First measurement	Last measurement	No. of follow-up studies
Normal subjects[c]	30	>4–52	–	3.8	2.7–4.5				
MPS type I	18	3–44	18.9	5.35	3.4–9.9	$P<0.01$	5.6	5.6	9
MPS type II	12	2–42	16.4	5.96	2.3–8.3	$P<0.01$	5.8	6.4	9
MPS type VI	35	2–42	13.6	6.71	3.0–9.2	$P<0.001$	6.2	5.9	19

[a] Mann-Whitney U-test.
[b] Mean observation period 2.9 years (range 1–9 years).
[c] Normal values from references 7 and 8.

where y is the SRC thickness in millimetres, and x is age in years.

ONS

Table 2 shows baseline and serial measurements of ONS diameter. When a widened ONS was due to increased intracranial pressure, morphological change in the optic nerve was apparent. With increased intracranial pressure of long duration, the initially tiny cyst-like liquid accumulations around the optic nerve (Figs. 4 and 5) expanded into larger lacunae. This corresponds to the increasingly dilated subarachnoid space.

Two patients with MPS type VI had a ventriculoperitoneal shunt for drainage of cerebral spinal fluid (CSF). In these patients, we observed a reduction in ONS diameter from 9.2 to 8.5 mm and 7.7 to 6.0 mm, respectively.

Frequency of papilloedema determined by US

Of 65 patients, 5 showed a prominent optic nerve head. One patient with MPS II had a 2-mm protrusion and dilatation of the ONS, but no dilatation of the SRC, and four patients with MPS VI had a protrusion up to 1.4 mm, all with dilatation of the ONS and one with dilatation of the SRC.

Optic nerve head morphology

As well as the normal shape of the optic nerve head, we recognized other patterns such as a tubular and a waist-like deformity at the level of the thickened SRC (Figs. 6 and 7). The thickness of the SRC in these patients measured at least 3 mm, and in one patient with MPS type II and two patients with MPS type VI the pattern was not concomitant with thickening of the ONS.

The ophthalmological findings are given in Table 3.

Discussion

Sonographic manifestations of MPS have been previously described in both cardiac and fetal US [2]. To the best of our knowledge, no US studies of the posterior chamber of the eye and optic nerve in these patients have previously been reported. The examination of the eyeball and optic nerve was performed in accordance with the established and reliable technique of transbulbar US. We observed four major morphological changes:

1. Thickened sclera.
2. Deformation of the optic nerve head.

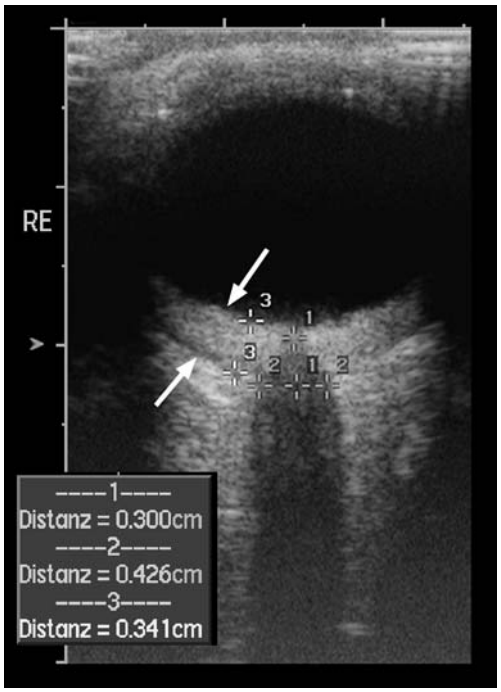

Fig. 3 Transbulbar US in a 33 year old shows thickened sclera (3.4 mm; *arrows*) with slight deformation of the optic nerve origin

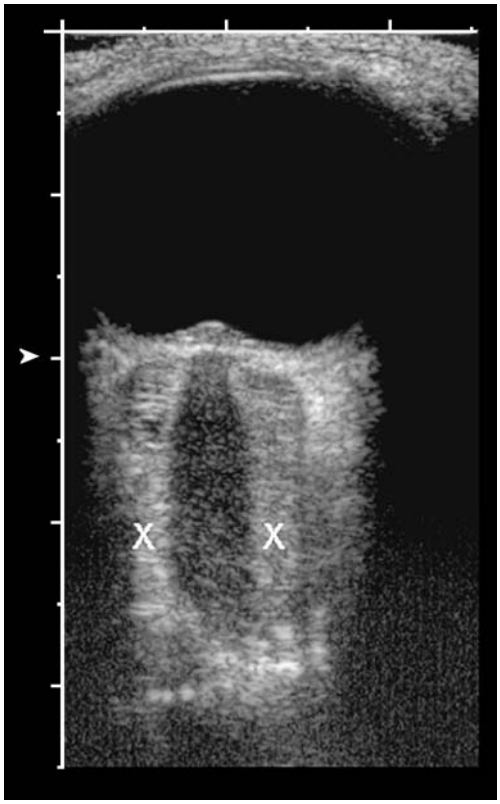

Fig. 4 Transbulbar US image in a 4-year-old child shows dilatation of the subarachnoid space with a more homogeneous pattern (*X*), prominent optic disc and indented posterior pole of the eye

3. Papilloedema.
4. Widening of the optic nerve and its sheath.

Sclera

By histopathological examination, the actual thickness of the normal sclera is 1 mm in the vicinity of the optic disc and 0.6 mm at the equator. The retina measures 0.1 mm at the fovea centralis and 0.56 mm near the optic disc [9, 10]. Using US we cannot discern the individual layers of the outer covering of the eyeball that is composed of the sclera, the uveal tract, and the retina. They appear as a thin, single band-like structure of homogeneous intermediate echogenicity (Figs. 1 and 2). In the vicinity of the optic disc we sonographically measured the total thickness of the outer cover (SRC) of the eye as 1.4–1.7 mm in healthy volunteers, which is in accordance with the sum of the single layers determined by histological measurements. Minor deviations from measurements as given in textbooks [9, 10] are within the range of US resolution.

The SRC was thickened to a variable extent in 45 of 65 patients examined, and in 20 patients, regardless of age, the thickness of the SCR was 2 mm or less. We found thicknesses between 1.4 and 4.2 mm while the mean values in patients with different types of MPS were much closer together (Table 1) with the lowest in those with MPS type I. Except in MPS type I, thickening of the SCR was statistically significant at initial examination. It is well

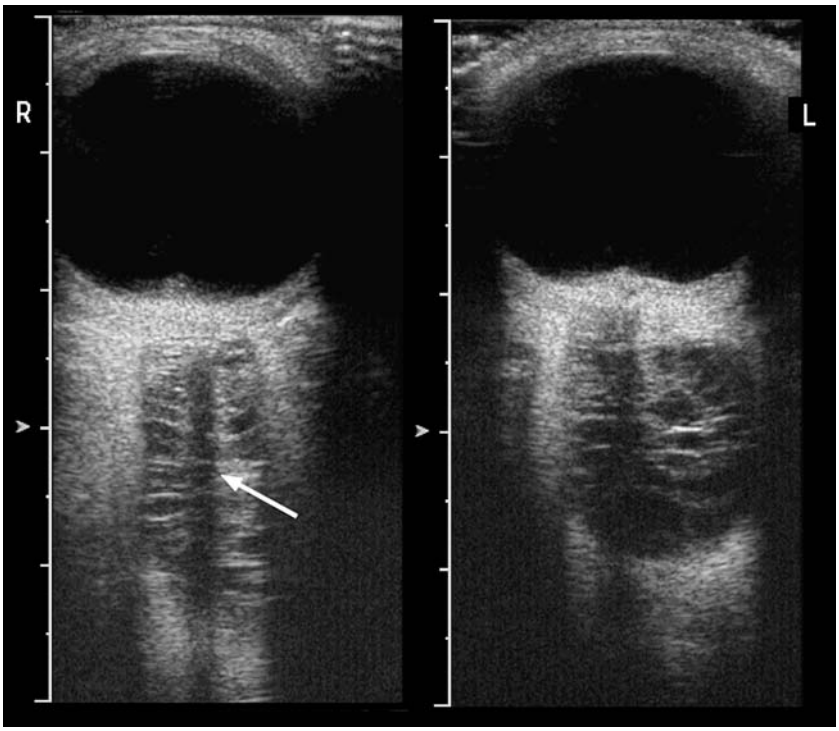

Fig. 5 Transbulbar US image in a 14-year-old child (*R* right eye, *L* left eye). There is cyst-like dilatation of the subarachnoid space on both sides, with a hump-like appearance on the left. Note the thin, atrophic optic nerve (*arrow*), thickened sclera, and prominent optic disc

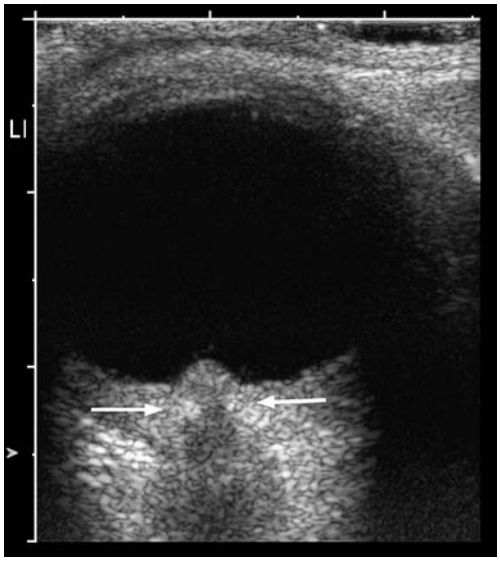

Fig. 6 Transbulbar US in a 25-year-old patient shows an hour-glass-like deformity of the optic nerve origin at the level of the lamina cribrosa (*arrows*). The optic nerve head is prominent

known that patients with subtypes Hurler/Scheie or Scheie have intermediate or mild ophthalmological symptoms. Where the SRC is slightly thickened, it has a band-like shape and is of homogeneous intermediate echogenicity (Fig. 4). Where the thickening is more pronounced, the SRC is sickle-shaped, with the greatest thickness located at the optic nerve head (Figs. 6 and 7). Thickening of the SRC is accentuated in the dorsal region of the eyeball, causing a change in the geometry of the eyeball.

In 24 patients the length of the optic axis was determined by optic interferometry. The mean ranged from 20.97 in patients with MPS type II to 20.37 mm in patients with MPS type VI. As a normal emmetropic eye has, depending on age, an axial length of 22.5–23.5 mm [11] the mean length of the visual axis is shortened by at least 1.5 mm (Table 3). Reduction of the visual axis by 1 mm results in hypermetropia of +3 dioptres. Therefore, the hypermetropia detected in our MPS patients was most probably the result of shortening of the visual axis due to storage of GAG in the sclera. At the very least, there seems to be a good correlation between thickening of the sclera, reduced length of the visual axis and the degree of hypermetropia (Tables 1 and 3).

Our data suggest that thickening of the sclera occurs very early and reaches its final extent at 2–4 years of age, which is normally the age when the disease is first diagnosed. During the period of observation there was little or no progression of widening of the SRC, and the average thickening of the sclera in the different groups appeared to be constant. Regardless of age, the range of thickening of the SRC was virtually constant with a wide variation in the single measurements as documented by the low Pearson correlation coefficient *r*. The gradient of the regression equation was very small. Using the regression equation for those with MPS type VI to hypothetically forecast the change in SRC thickness reveals an increase in SRC thickness of only 0.36 mm in 20 years. This value is near the limit of resolution of our US equipment and thus minimal. ERT does not have a sonographically detectable effect on the thickness of the sclera. It is possible that tissue with a low metabolic turnover like cartilage, tendons, and fascia is, in principle, immune to therapy.

Optic nerve head – papilloedema

The sonographic shape of the optic nerve head in healthy people resembles a Gothic arch or semicircle (Figs. 1 and 2). In MPS patients we identified two additional findings: deformation and protrusion. Papilloedema may be a diagnostic sign in patients with increased intracranial pressure, but there are other causes such as optic neuritis, anterior ischaemic optic neuropathy, as well as drusen of the optic nerve head. In three patients without signs of elevated intracranial pressure we found either a conical or waist-like deformity with protrusion of the optic nerve head at the level of the thickened sclera (Figs. 6 and 7). We assume that the thickened sclera causes this deformation of the optic nerve head. This assumption is supported by histological studies showing that in MPS patients the lamina cribrosa, as part of the sclera, is also thickened [11, 12], and the optic nerve head undergoes deformation. Impingement of the optic nerve at the passage of the lamina cribrosa may lead to a swollen disk as in hydrocephalus, but in these cases it is not a sign of increased

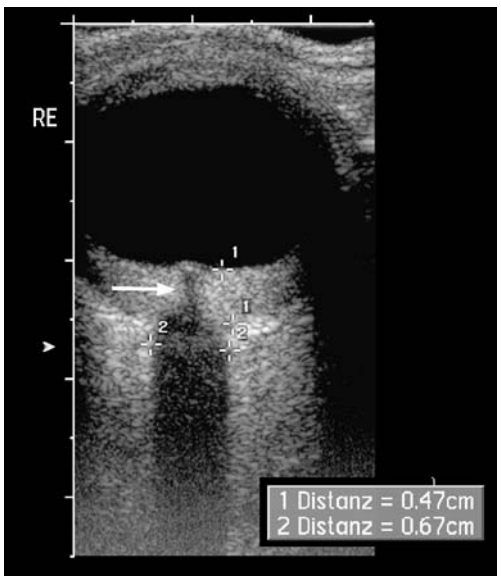

Fig. 7 Transbulbar US in a 25-year-old patient shows thickening of the SRC (4.7 mm) and ONS (6.7 mm). Note the tubular narrowing and elongation of the optic nerve head (*arrow*)

Table 3 Length of visual axis and refraction in patients with MPS II and MPS VI

Subject		No. of subjects	Age (years)		Visual axis (mm)		Refraction (spherical equivalent in dioptres)
			Mean	Range	Mean	Range	
Normal[a]	Child	–	4	–	22.5	–	–
	Adult	–	–	–	23.5	–	–
MPS type II		18	16.9	7–41	20.97	19.39–23.41	0 to +5.25
MPS type VI		6	20.8	8–44	20.37	19.65–20.76	0.5 to +7.5

[a] Normal values for children and adults from reference 11.

intracranial pressure. Additionally, such morphological deformation strengthens the hypothesis that impingement of the axons within the lamina cribrosa may contribute to optic nerve atrophy [2].

In five patients we identified a swollen disc due to increased intracranial pressure (hydrocephalus with dilation of the ONS), a well-known complication of MPS. After implantation of a ventriculoperitoneal shunt in two patients with MPS type VI, the ONS diameter diminished.

Optic nerve sheath

Studies have proved that dilatation of the subarachnoid space of the optic nerve due to increased intracranial pressure occurs within several minutes and parallels the pressure increase. In contrast, papilloedema takes days to form and to recede [8, 13, 14]. Only 5 out of 50 of our patients with dilatation of the ONS showed papilloedema. In 3 out of 50 patients a thickened SRC was concomitant with papilloedema. Thus we can assume that for the single sonographically detectable morphological finding of papilloedema, at least two different pathomechanisms are responsible in varying degrees: intracranial hypertension and impingement of the optic nerve at the level of the lamina cribrosa.

Under normal circumstances the subarachnoid space surrounding the optic nerve is so narrow that US cannot depict fluid in this space (Fig. 1). The subarachnoid space may particularly expand directly behind the eyeball [6]. With increasing intracranial pressure, initially tiny cyst-like liquid accumulations emerge (Fig. 4). Accumulation of liquid in the subarachnoid space of the optic nerve is proof that CSF is able to pass through the optic canal and that there is nothing to obstruct flow in this region. Here it can be viewed as a sign of increased intracranial pressure [8, 13]. With higher pressure, the CSF merges into larger lacunae. This corresponds to a massively dilated subarachnoid space divided by tiny trabeculae (Fig. 5), which can be depicted easily by US [7, 8]. The increase in ONS diameter appears to occur early in the course of the disease because the mean values are already statistically significantly increased at the initial examination (Table 2).

Similarly as constant as the dilatation of the SRC was that of the ONS during the time of observation. In some patients we observed an increase in the diameter parallel to the progression of their communicating hydrocephalus. This finding is paralleled by the histologically proven deposition of GAG in the meninges of the optic nerve [12, 15]. This mechanism may contribute to optic nerve atrophy in these patients. Stürmer [12] proposed from histological observations a mechanical irritation of the optic nerve in the optic canal through the storage of GAG in the subdural and subarachnoid spaces. Atrophy of the optic nerve may develop in all MPS types and is diagnosed ophthalmologically. Atrophy can only be detected sonographically in cases where the optic nerve has become very thin (Fig. 5).

Due to the different pathomechanisms leading to dilatation of the ONS (deposition of GAG, increased intracranial pressure), and unidentified reasons in specific cases, we did not calculate the mean values under ERT that influence at most only one factor. Based on ophthalmological and our sonomorphological findings, we suggest the following pathomechanisms singly or in combination as the cause of optic nerve atrophy: glaucoma, dystrophy of the retina, impingement of the optic nerve head, dilatation of the subarachnoid space of the optic nerve due to storage of GAG or due to increased intracranial pressure, and narrowing of the optic canal. ERT does not alter the sonomorphological findings of the eye; this is in sharp contrast to other symptoms such as stiffening of joints [3–5].

In addition to the inherent biases due, in part, to the retrospective nature of this study, other limitations are gaps in clinical data and lack of a tool that could serve as a reference for assessment of US findings and measurements. For these reasons we applied statistical evaluation of our data with great caution.

Conclusion

The sonographic findings of the eye in patients with MPS types I, II, and VI revealed significant thickening of the

ONS to 4.0–12 mm, and of the sclera to 2.0–2.6 mm (on average). It appears that this thickening did not increase with age. Thus our findings lead us to believe that the changes in the eyes of patients with MPS develop very early, before diagnosis of the disease. The results of sonomorphological examinations led to a possible clarification of the hypermetropia as well as the pathomechanism contributing to atrophy of the optic nerve. ERT does not result in measurable regression or other changes in the morphological findings of the eye and optic nerve.

References

1. Baehner F, Schmiedeskamp C, Krummenauer F et al (2005) Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis 28:1011–1017
2. Ashworth JL, Biswas S, Wraith E et al (2006) Mucopolysaccharidoses and the eye. Major review. Surv Ophthalmol 51:1–17
3. Wraith JE, Clarke LA, Beck M et al (2004) Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human α-L-iduronidase (laronidase). J Pediatr 144:581–588
4. Muenzer J, Wraith JE, Beck M et al (2006) A phase II/III clinical study of enzyme replacement therapy with idursulfatase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 8:465–473
5. Harmatz P, Giugliani R, Schwartz I et al (2006) Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 148:533–539
6. Helmke K, Hansen HC (1996) Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension. I. Experimental study. Pediatr Radiol 26:701–705
7. Helmke K, Hansen HC (1996) Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension. II. Patient study. Pediatr Radiol 26:706–710
8. Brzezinska R, Schumacher R (2002) Diagnosis of elevated intracranial pressure in children with shunt under special consideration of transglobe sonography of the optic nerve. Ultraschall Med 23:325–332
9. Berry MM, Standring SM, Bannister LH (1995) Nervous system. In: Williams PL (ed) Gray's anatomy, 38th edn. Churchill Livingstone, New York, p 1322
10. Funke RH, Appel DJ, Naumann GO (1997) Embryologie, Anatomie und Untersuchungstechnik. In: Doerr W, Seifert G, Uehlinger E (eds) Spezielle pathologische Anatomie: Pathologie des Auges I. Springer, Berlin, pp 1–93
11. Sampaolesi R (1981) Ocular echometry in the diagnosis of congenital glaucoma. Doc Ophthalmol Proc Series 29:177–189
12. Stürmer J (1989) Mukopolysaccharidose Typ VI-A (Morbus Maroteaux-Lamy). Klin Monatsbl Augenheilkd 194:273–281
13. Hansen HC, Helmke K, Kunze K (1994) Optic nerve sheath enlargement in acute intracranial hypertension. Neuroophthalmology 14:345–354
14. Hansen HC, Helmke K (1997) Validation of the optic nerve sheath response to changing cerebrospinal fluid pressure: ultrasound findings during intrathecal infusion tests. J Neurosurg 87:34–40
15. Collins ML, Traboulsi EI, Maumenee IH (1990) Optic nerve head swelling and optic atrophy in the systemic mucopolysaccharidoses. Ophthalmology 97:1445–1449