

## Clinical characterization of cardiovascular abnormalities associated with feline mucopolysaccharidosis I and VI

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**Summary Objective:** The purpose of this study was to define the cardiovascular abnormalities present in young and adult cats affected with the lysosomal storage diseases mucopolysaccharidosis (MPS) I and MPS VI. **Method:** Eighteen cats affected with MPS I and 10 cats affected with MPS VI were evaluated by physical examination, electrocardiography and echocardiography. Electrocardiography (ECG) was performed on all MPS I and 9 of the MPS VI cats. Twelve unaffected cats underwent complete examinations for comparison purposes. **Results:** No cardio-

vascular abnormalities were noted on physical examination. Measured ECG intervals were normal in affected cats; however, sinus arrhythmia was noted more frequently than in the unaffected cats. Significant echocardiographic abnormalities included aortic valve thickening, regurgitation and aortic root dilation. Significant mitral valve thickening was also noted. The severity of changes increased in older affected cats. **Conclusion:** As affected animals increased in age, more cardiac abnormalities were found with increasing severity. Significant lesions included the mitral and aortic valves and ascending aorta, but myocardial changes were not recognized. MPS I and MPS VI cats have similar cardiovascular findings to those seen in children and constitute important models for testing new MPS therapies.

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### Abbreviations

2D two-dimensional  
ECG electrocardiography  
GAG glycosaminoglycans  
MPS mucopolysaccharidosis

### Introduction

The mucopolysaccharidoses (MPS) are a family of lysosomal storage diseases resulting from defective catabolism of glycosaminoglycans (GAGs). In children affected with MPS, the most common cardiovascular lesion is thickening of the mitral valve secondary to GAG accumulation in the valve leaflets, resulting in

fibrosis and nodular deformation (Sammarco et al 2000). However, cardiomyopathy and myointimal proliferation of epicardial coronary arteries has also been described in humans secondary to GAG accumulation (Braunlin et al 2006). Lesions are progressive with risk of death resulting from congestive heart failure (Dangel 1998). The overall incidence is 1 in every 7700 live births (Meikle et al 1999).

Cardiovascular abnormalities seen by echocardiography have been reported previously in a colony of MPS VII ( $\beta$ -glucuronidase-deficient) dogs including: mitral valve thickening and regurgitation, increased aortic diameter, and thickening and regurgitation of the aortic valve (Ponder et al 2002; Sammarco et al 2000; Sleeper et al 2004). Similar findings were noted in cats affected with MPS I and VI on postmortem examination (Haskins et al 1979a, b), and disordered elastic fibres and smooth-muscle cells have previously been recognized histologically in MPS VI affected feline aortas (Bielicki et al 1999); however, antemortem cardiovascular findings have not been reported.

MPS I (Hurler, Scheie, Hurler/Scheie syndrome,  $\alpha$ -L-iduronidase deficiency) is caused by a 3 bp deletion resulting in deficiency of the hydralase and multisystem accumulation of heparan and dermatan sulfates (Kakkis et al 2001). MPS I cats have less than 3% of normal serum activity of  $\alpha$ -L-iduronidase (Ponder et al 2006). MPS VI (Maroteaux-Lamy syndrome, 4-sulfatase deficiency) leads to accumulation of dermatan sulfate (Norrdin et al 1995). Feline MPS VI results from a point mutation at amino acid residue 476 (Ellinwood et al 2004) resulting in less than 5% of catalytic capacity of the enzyme (Brooks et al 1997). Myoblasts from affected cats store approximately 7 times as much GAGs as normal cats (Yogalingam et al 1996). The purpose of this study was to compare electrocardiographic and echocardiographic data from young and old MPS I and MPS VI cats with those obtained from unaffected cats.

## Methods

Colonies of cats affected with MPS I and VI were established at the University of Pennsylvania, School of Veterinary Medicine. Animals were raised under National Institutes of Health and US Department of Agriculture guidelines for the care and use of animals in research. Eighteen cats affected with MPS I and 10 with MPS VI were evaluated by physical examination and electrocardiography (9 of the MPS VI cats

had ECG) using a Hewlett-Packard Page Writer (Sacramento, CA, USA). Six-lead electrocardiograms (the limb leads) were obtained and the PR, QRS, and QT intervals and mean electrical axis were measured. Cardiac rhythm was also assessed.

Complete echocardiograms (including 2D, M-mode, and colour flow Doppler of all valves) were obtained from all but one MPS I cat, using a Philips 7500 Sonos ultrasound machine (Wilmington, MA, USA) and a 12 MHz transducer. For the echocardiographic assessment, 22/28 affected cats were sedated with butorphanol (0.3–0.5 mg/kg) intramuscularly. Two also received diazepam (0.15–0.2 mg/kg) intramuscularly. Sedation was not necessary in any of the unaffected cats. Left ventricular measurements obtained included the inter-ventricular diastolic septal thickness, left ventricular diastolic free wall thickness, and diastolic and systolic left ventricular chamber diameter. From the right parasternal, short-axis view, the left atrial and aortic dimensions were obtained from the first diastolic frame in which closure of the aortic valve was evident (at the level of the sinus of Valsalva) as previously described (Abbott and MacLean 2006; Rishniw and Erb 2000). The aortic diameter was also measured in the long axis at the sinotubular junction (distal to the sinus of Valsalva) during diastole. All measurements were obtained using the leading edge to leading edge technique as recommended by the American Society of Echocardiography (Weyman 1994). A fractional shortening was calculated to assess systolic function using the formula: (left ventricular diastolic diameter minus left ventricular systolic diameter)/ (left ventricular diastolic diameter). All valves were interrogated with colour flow Doppler and pulsed-wave Doppler. A subjective score was assigned for thickness of the mitral and aortic valves, loss of aortic narrowing at the sinotubular junction in the long-axis plane, and valvular regurgitation (aortic and mitral). Increased echogenicity and/or thickening of the valve leaflets was used to develop this subjective valve thickening grade. The subjective scores ranged from 0 to 4 with 0 = normal/none; 4 = severe. Twelve unaffected, but related cats underwent the same cardiac evaluations for comparison purposes. All examinations were performed by the same sonographer, who was blinded to status of the subject. More than one examination was available for 1 MPS I affected cat and 3 MPS VI affected cats. For statistical analysis, only data from the oldest time point was included.

To compare disease (MPS VI, MPS I, unaffected cats) and age groups ( $\leq 12$  months,  $> 12$  months) with

regard to electrocardiography parameters, a 2-way analysis of variance was performed. To determine differences between affected and unaffected cats adjusting for age, a 2-way analysis of variance was performed. To adjust for multiple pairwise comparisons the Tukey–Kramer method was used. All analyses were performed using SAS statistical software (Version 9.1, SAS Institute, Cary, NC, USA). Because lesions associated with enzyme storage progress with age in MPS, additional statistical analysis was performed in order to evaluate this relationship with regression modelling. ANOVA with Tukey post-hoc analysis or Student's *t*-test was used to compare values in different groups using Sigma Stat software (Systat Software, Inc., Point Richmond, CA, USA). For this analysis, echocardiographic data from multiple time points were included from 4 cats (1 MPS I and 3 MPS VI cats). The statistical significance of the correlation coefficient ( $R^2$ ) was determined by calculation of the *t* statistic using the formula  $t=R$  divided by the square root of  $[(1 - R^2)/(n - 2)]$ , and comparison with a table to determine the *p*-value (Donnelly 2004).

## Results

### Group age parameters

Mean ages of the younger group of normal, MPS I and MPS VI cats was 10.9, 10.5 and 9.3 months, while the mean age of the older groups was 46.0, 20.6 and 39.0 months, respectively.

### Cardiovascular physical examination

No cardiovascular abnormalities were detected on physical examination of normal, affected MPS I, or

affected MPS VI cats. However, all but one MPS I cat was purring loudly during examination, which would have made auscultation of a cardiac murmur unlikely. In these cats, even the normal heart sounds (S1 and S2) were not detectable over purring sounds. However, femoral pulse quality, mucous membrane colour, and capillary refill time were normal in all cats.

### Electrocardiography

All measured intervals were within the normal range for the species. Three of the MPS I cats and six of the MPS VI cats had a sinus arrhythmia; however, a regular sinus rhythm was present in all 12 unaffected cats ( $p = 0.0004$ ). The mean electrical axis was deviated anteriorly in 3 of the 12 unaffected cats, in 4 of the 18 MPS I cats, and in 4 of the 9 MPS VI cats, which were not significantly different. Three of the MPS I cats had QRS notching, but none of the MPS VI or normal cats did. Electrocardiographic interval measurements are presented in Table 1.

### Echocardiography

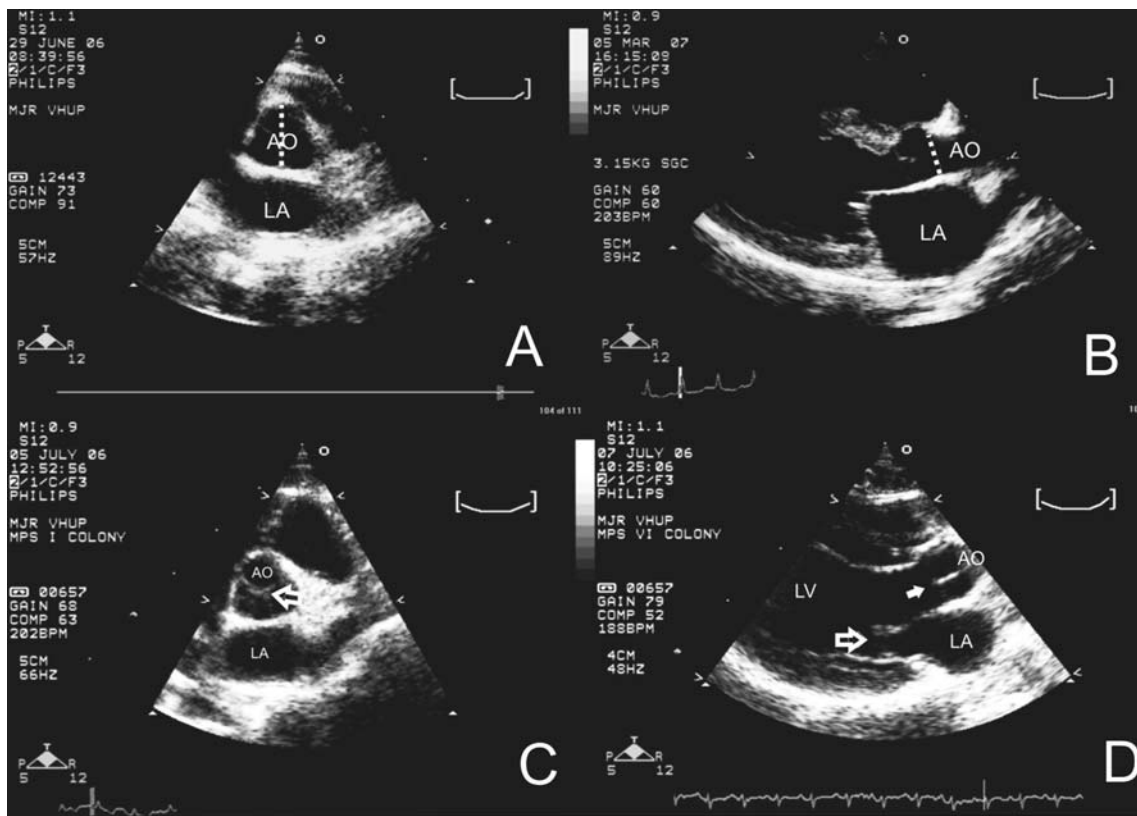
Echocardiographic measurements obtained that were within normal limits for the species (data not shown) (Boon 1998) included the left ventricular systolic and diastolic chamber diameters, diastolic left ventricular wall thickness, and left atrial diameter. Significant findings included aortic root enlargement, and mitral and aortic valve thickening. Aortic diameters were measured in the short axis at the level of the sinus of Valsalva (Fig. 1A) and in the long axis at the sinotubular junction (Fig. 1B). No difference was found between young and old unaffected cats at any time point (Figs. 2 and 3). However, when cats were

**Table 1** Electrocardiographic interval measurements in MPS I and MPS VI cats. All of the measurements were within normal limits for this species

	Age (months)	<i>N</i>	HR (bpm)	PR (s)	QRS (s)	QT (s)
Unaffected	≤12	6	171±26	0.08±0.005	0.05±0.005	0.18±0.024
	>12	6	198±25	0.07±0.007	0.04±0.005	0.17±0.017
MPS I	≤12	8	211±18	0.07±0.007	0.03±0.008	0.15±0.015
	>12	10	214±36	0.07±0.008	0.04±0.012	0.16±0.027
MPS VI	≤12	4	195±25	0.09±0.011	0.04±0.010	0.18±0.016
	>12	5	198±33	0.08±0.013	0.04±0.006	0.15±0.062

ECG measurements: mean ± standard deviation.

Normal feline ECG ranges: HR, 160–240 bpm; PR, 0.05–0.09 s; QRS, maximum of 0.04 s; QT, 0.12–0.18 s.



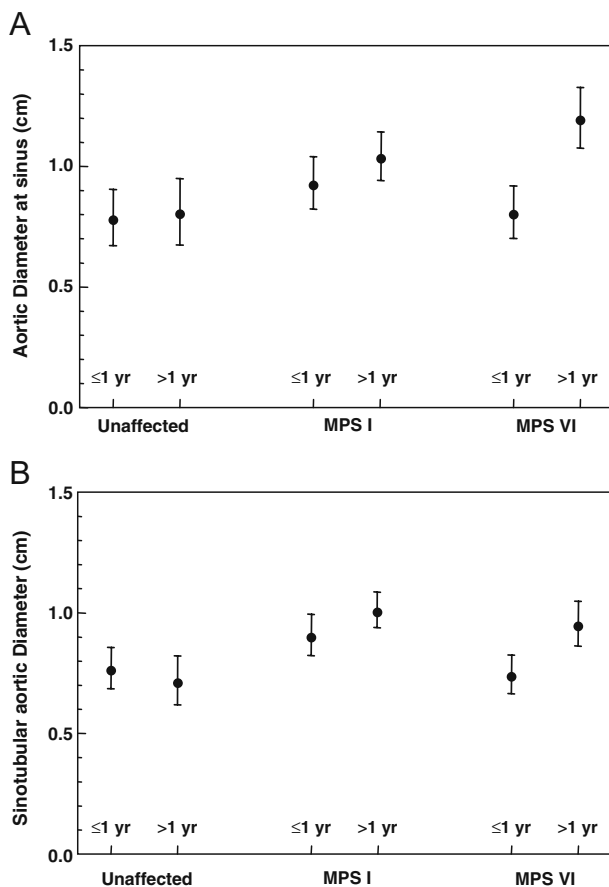
**Fig. 1** (A) A short-axis right parasternal echocardiogram from an unaffected cat showing where the aortic diameter is measured at the level of the aortic valve (white line). (B) A long-axis right parasternal echocardiogram from an unaffected cat showing the sinotubular junction, the aortic region most frequently dilated in cats with MPS I and VI. (C) A right parasternal short-axis

echocardiogram obtained at the heart base. Note the severely thickened aortic valve (arrow) compared with the unaffected cat in (A). (D) A right parasternal long-axis echocardiogram. Note the thickening of the mitral (black arrow) and aortic (white arrow) valves compared with the unaffected cat in (B). AO = aorta; LA = left atrium; LV = left ventricle

older than 12 months of age, the aorta measured significantly larger in MPS VI ( $1.2 \pm 0.3$  cm) and MPS I ( $1.1 \pm 0.1$  cm) cats than in unaffected cats ( $0.81 \pm 0.1$  cm) at the sinus of Valsalva level ( $p = 0.003$  for unaffected vs. MPS VI;  $p = 0.008$  for unaffected vs. MPS I). Also, at the sinotubular junction older MPS I ( $1.0 \pm 0.2$  cm) and MPS VI ( $0.96 \pm 0.1$  cm) affected cats were significantly dilated compared to unaffected cats ( $0.72$  cm  $\pm$  0.1;  $p < 0.0001$  for unaffected vs. MPS I;  $p = 0.002$  for unaffected vs. MPS VI) (see Fig. 2). The linear regression formula shows that the aortic diameter increases by about 0.1 cm per year for the MPS I and MPS VI cats.

Subjective echocardiographic assessments were scored from 0 (normal or none) to 4 (severe). Significant mitral valve thickening was noted in young MPS I ( $1.75 \pm 0.5$ ) versus young unaffected cats ( $0.29 \pm 0.8$ ;  $p = .001$ ), and in both older affected groups (unaffected cats:  $0 \pm 0$ ; MPS I:  $1.1 \pm 0.8$ ; MPS VI:  $1.3 \pm 0.4$ ;  $p = .04$  for unaffected vs. MPS I;  $p < .0001$  for unaffected vs. MPS VI). Significant aortic valve

thickening was present in both groups of young, affected cats (unaffected cats  $0 \pm 0$ ; MPS I  $1.6 \pm 0.7$ ; MPS VI  $1.0 \pm 0.5$ ;  $p = .0002$  for unaffected vs. MPS I;  $p = 0.04$  for unaffected vs. MPS VI). Older affected cats also had significant thickening (unaffected cats  $0 \pm 0$ ; MPS I  $1.6 \pm 0.8$ ; MPS VI  $2.1 \pm 0.7$ ;  $p < 0.0001$  for unaffected vs. MPS I;  $p < 0.0001$  for unaffected vs. MPS VI) and thickening worsened with age in the MPS VI cats ( $p = 0.01$ ). Subjective assessment of loss of aortic sinotubular narrowing scores were similar in all groups of young cats (unaffected  $0 \pm 0$ ; MPS I  $0.13 \pm 0.4$ ; MPS VI  $0.13 \pm 0.4$ ), but the score was significantly greater in the older affected groups compared with the unaffected cats (unaffected  $0 \pm 0$ ; MPS I  $1.1 \pm 1.0$  [ $p = 0.004$ ]; MPS VI  $1.43 \pm 1.0$  [ $p = 0.007$ ]). Moreover, dilatation worsened with age in MPS I ( $p = 0.003$ ) and MPS VI ( $p = 0.005$ ) (see Fig. 3). An aortic aneurysm was noted in the ascending aorta of one MPS I cat evaluated at 2.5 years of age (Fig. 4). No significant difference between groups was found for mitral or aortic regurgitation (data not shown). Figure 5 displays the

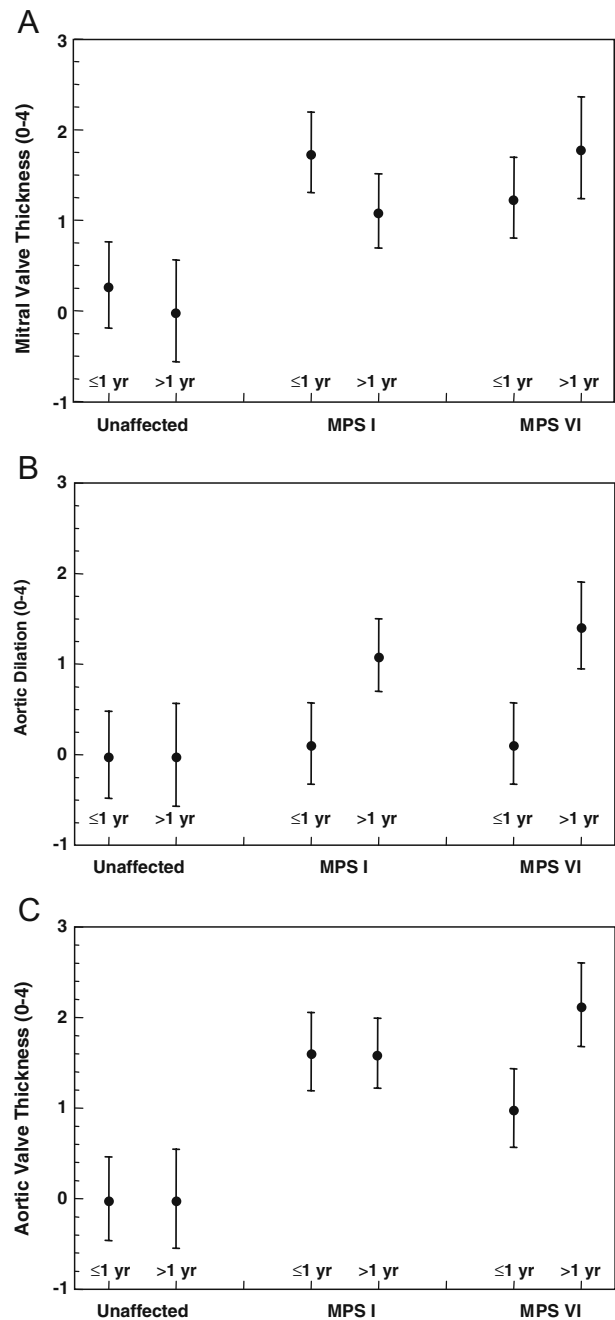


**Fig. 2** Aortic diameter measurements in affected and unaffected cats. (A) Aortic dilation at the sinus of Valsalva was present in MPS VI cats ( $p=0.003$ ) and MPS I cats ( $p=0.008$ ) older than 1 year compared with similarly aged unaffected cats. (B) Aortic dilatation at the sinotubular junction was present in MPS I ( $p=0.0009$ ) and MPS VI ( $p=0.002$ ) cats older than 1 year compared with similarly aged unaffected cats

regression analysis for changes in aortic diameters and mitral and aortic valve thickening over time in all cats and shows that aortic dilation worsens with age.

## Conclusions

The mucopolysaccharidoses (MPS) are a family of lysosomal storage diseases resulting from defective catabolism of GAGs. The disease occurs naturally in the mouse, rat, dog, cat, goat, and emu (Ellinwood et al 2004). Because the disease phenotype is very similar to that seen in children, dogs and cats represent excellent models for assessing the therapeutic efficacy of various techniques. In fact, studies have already evaluated therapeutic approaches in these models (Kakkis et al 2001; Ponder et al 2006; Sleeper et al 2004; Traas et al 2007) and physical, biochemical, and pathological findings in affected cats have been described (Haskins et al 1979a, b, 1983). One study



**Fig. 3** Subjective echocardiographic assessment of mitral valve thickness, aortic valve thickness and aortic dilatation. Note that there is no difference associated with ageing in the unaffected cats. Range: 0 = normal/none; 4 = severe. (A) Significant mitral valve thickening was present in young ( $p=0.001$ ) and old ( $p=0.04$ ) MPS I cats compared with unaffected cats of the same age. Significant valve thickening was present in older MPS VI cats compared with older unaffected cats ( $p=0.0001$ ). (B) Significant subjective aortic dilatation was present in older MPS I ( $p=0.0004$ ) and MPS VI ( $p=0.0007$ ) cats compared with unaffected cats. Dilatation was significantly worse in older affected cats of both groups (MPS I  $p=0.003$ ; MPS VI  $p=0.005$ ). (C) Significant aortic valve thickening was present in young ( $p=0.0002$ ) and old ( $p<0.0001$ ) MPS I cats and young ( $p=0.04$ ) and old ( $p<0.0001$ ) MPS VI cats compared with unaffected cats of the same age. Thickening worsened with age in the MPS VI cats ( $p=0.01$ )



measured intervals were within the normal range for the species. The difference is believed to be clinically insignificant and was not present in older animals. Likewise, the QRS notching noted in three MPS I affected cats was deemed insignificant based on the presence of normal QRS durations in these cats. Noted significant ECG abnormalities in affected cats included the presence of sinus arrhythmia. The significance of this arrhythmia is unclear, but it is a rare finding in cats, a species in which the stress of restraint for ECG often results in a regular sinus rhythm or sinus tachycardia. Its presence was not associated with obvious echocardiographic or gross pathological myocardial thickening or scarring, but it is possible that myocardial GAG storage affected the sinus node, resulting in altered automaticity. Further histological evaluation, particularly focusing on the cardiac conduction pathway, is warranted. Electrocardiographic changes have been reported in one relatively large study of MPS VI children, with 74% having ECG changes (11% with a sinus arrhythmia) (Azevedo et al 2004). The reasons for ECG changes in affected children have not been elucidated.

Echocardiographic findings are consistent with previous pathological reports of affected cats (Haskins et al 1979b, 1983). Specifically, aortic and mitral valve thickening (Fig. 1C and D) and aortic dilatation with loss of narrowing at the sinotubular junction was often present and increased in severity with age. The progression with age was more dramatic in the MPS VI than in the MPS I affected cats. However, the aged group of MPS VI cats was older than the aged group of MPS I cats (mean ages of 39 vs. 21 months). This discrepancy in mean ages likely skewed the results since lesion severity worsens with age. Furthermore, the linear regression curve supports this assumption by showing that the progression over time is similar between the affected groups. Similar findings have also been reported in MPS VII dogs (Haskins et al 1982; Ponder et al 2002). Previously, the accumulation of dermatan sulfate has been linked to impaired elastic fibre production and development of progressive coronary artery intimal thickening in children with Hurler disease (Hinek and Wilson 2000). Another study found that soluble heparan sulfate inhibits elastic fibre assembly by inhibiting tropoelastin association with the extracellular matrix (Kozel et al 2004). This suggests that aortic dilatation in cats affected with MPS I and VI may be progressive because storage of these glycosaminoglycans and impaired elastogenesis increases with age. Alternatively, elastin degradation may be the causative factor as suggested in a murine model of MPS I (M.A. Xiucui and K.P. Ponder, unpublished data, 2008).

The only cat noted to have an aortic aneurysm was an MPS I animal examined at a relatively older age (2.5 years). Aortic aneurysms in the paediatric population are rare; however, they have been reported in a child affected with an unclassified MPS (Engle et al 1997). MPS was presumed because chondroitin sulfate and heparan sulfate were detected with urine electrophoresis, but a definitive diagnosis of MPS type was not reported. Ours is the first aortic aneurysm reported in a dog or cat with MPS.

One limitation of the study of this report is the difficulty in blinding the sonographer to group status. Although status of individual cats was unknown, conventional echocardiography cannot be performed under truly masked conditions because MPS affected cats usually have obvious clinical features, including facial deformity and gait abnormalities. These clinical features have been described previously (Haskins et al 1979b, 1983) and are similar to those seen in children. As our data show, MPS I and MPS VI cats also develop similar cardiovascular lesions to those seen in affected children. This similarity, the relatively slow progression of clinical decompensation, and a body size closer to children than the rodent models make these feline models excellent options for assessing potential therapeutic approaches.

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