Am. J. Hum. Genet. 43:726–732, 1988

Dural Ectasia Is a Common Feature of the Marfan Syndrome

Reed E. Pyeritz,* Elliot K. Fishman,† Barbara A. Bernhardt,* and Stanley S. Siegelman†

*Division of Medical Genetics, Department of Medicine, and †Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore

Summary

Widening of the lumbosacral spinal canal was found in 63% of 57 patients with the Marfan syndrome and in none of 57 age- and sex-matched non-Marfan control patients, who underwent CT scanning for routine clinical indications. The bony abnormalities in mild cases consisted of thinning of the pedicles and taminae and erosion of the neural foraminae and were generally limited to L5 and S1. More severe changes were present in 13 patients, two of whom had associated neurologic signs, and included meningoceles or near total erosion of a pedicle. Presence and severity of vertebral abnormalities were associated with neither any other clinical feature nor overall phenotypic severity. Dural ectasia can be added to the list of pleiotropic manifestations of the Marfan syndrome.

Introduction

The phenotype caused by a mutation in a single genetic locus is often pleiotropic, in that multiple, perhaps superficially unrelated, abnormalities appear in diverse organs and tissues. In the absence of biochemical or genetic tests for the fundamental defect, diagnosis rests on detecting sufficient clinical features to satisfy the empiric criteria for a particular syndrome. Such is the case with the Marfan syndrome, an autosomal dominant disorder in which a presumed aberration in a component of connective tissue produces numerous manifestations. Although diagnosis relies on characteristic features in the eye, skeleton, heart, and aorta (Pyeritz and McKusick 1979; Pyeritz 1986), other organs are also affected, including skin (McKusick 1972; Pyeritz 1986), lung (Hall et al. 1984; Streeten et al. 1987), and perhaps muscle (Pages et al. 1985; Clericuzio et al. 1986).

After encountering several patients with Marfan syndrome who had radicular pain associated with sacral meningoceles (Fishman et al. 1983), we conducted a prospective study of the spine to estimate the frequency and variability of dural abnormalities.

Received December 14, 1987; revision May 24, 1988.

Address for correspondence and reprints: Reed E. Pyeritz, M.D., Ph.D., Blalock 1012, Johns Hopkins Hospital, Baltimore, MD 21205.

0002-9297/88/4305-0019$02.00

Methods

Study Population

Diagnosis of the Marfan syndrome was based on standard criteria (Pyeritz and McKusick 1979; Pyeritz 1986); in no case did the presence of dural ectasia contribute to the diagnosis. All 57 subjects had a clinical indication for computed tomography (CT) of their thorax and abdomen; 30 males and 12 females had had composite graft repair of the ascending aorta (Gott et al. 1986) and underwent routine evaluation of their entire aorta; eight males and five females were suspected of aortic dissection or aneurysm; and two females had radicular neurologic symptoms. None of the patients reported elsewhere (Fishman et al. 1983) is included in the present study. All CT studies were performed between 1979 and 1987.

Patients who did not have a heritable disorder of connective tissue were selected from among all patients who underwent CT scan of the abdomen and pelvis during 1979–87. Aside from ensuring the same ratio of males to females and the same age distribution as among the Marfan patients, selection of these control patients was random.

A control group comprising patients with the Marfan syndrome was established for comparison of overall phenotypic severity. After a review of the list of all patients with the Marfan syndrome that were seen in our outpatient clinic, beginning with the most recently seen

and working back in time, a control patient was matched, by sex and age (within 3 years), for each of the Marfan subjects studied by CT.

Assessment of Phenotypic Severity

To address the issue of bias of selection, we developed for the present study a quantitative phenotype measure that was based on both the number of pleiotropic features present (excluding dural ectasia) and their qualitative severity. For example, an aortic root diameter normal for body surface area was worth no points, dilatation ≤50 mm was worth 1 point, dilatation >50 mm was worth 3 points, and aortic dissection was worth 2–4 points, depending on extent. The overall maximum score was 76. This scoring system has not yet been subjected to validation; a copy is available on request to R.E.P. Information for calculation of the total severity score was obtained by review of the medical records; no points were added when a specific phenotypic feature was not mentioned in the record.

Computed Tomography and Analysis of Results

A Siemens DR3 scanner was used for all examinations, with settings of 125 kV, 3.2s, 230 mAs, and a slice thickness of 4 or 8 mm. In the first analysis, the films of all patients with the Marfan syndrome were viewed in a random order and interpreted by one radiologist (E.K.F.) who had no knowledge of patients' symptoms or severity scores. The vertebral column from the upper cervical through the coccygeal regions was examined in each case. Patients were graded for presence and extent of (1) widening of the neural canal, (2) thinning of the bony cortex of the vertebral bodies and pedicles, (3) dilatation of neural foramina, and (4) protrusion of dura outside the neural canal. Dural ectasia was judged to be present when any one of these abnormalities existed. To be labeled severe dural ectasia, a meningocele or near total erosion of one pedicle was required.

During a second session, films of both the Marfan and the control patients were viewed in random order by the same radiologist. Comparison was made of the two interpretations of the studies of the Marfan patients to determine intraobserver variability.

Statistics

Differences between group means and between paired data were assessed for significance by Student's *t*-test (two-tailed).

Results

Frequency and Severity of Dural Ectasia

Thirty-six patients (63%), including 24 men and 12 women, had dural ectasia (table 1). The most common criteria were widening of the neural canal and thinning of the pedicles in the lower lumbar and upper sacral region (fig. 1). In seven male and six female patients,

Table 1

Characteristics of Marfan Patients and Controls

Group (*N*)	Mean, SD	
	Age (years)	Severity Score
Marfan patients who had CT (57):		
All males (38)	34.3, 11.3	28.4, 6.4[a]
With dural ectasia (24)	31.8, 8.5[b]	29.7, 6.9
Without dural ectasia (14)	38.7, 14.3[b]	26.3, 4.8
All females (19)	39.4, 12.1	26.1, 6.8[c]
With dural ectasia (12)	41.1, 10.7	25.3, 7.3
Without dural ectasia (7)	38.3, 13.2	27.4, 6.2
Marfan patients who did not have CT (57):		
Males (38)	34.1, 11.2	20.9, 6.1[a]
Females (19)	38.8, 11.1	20.4, 5.8[c]
Non-Marfan patients who had CT (57)	36.3, 12.8	

Note.—Except for those indicated by the lettered footnotes below, all relevant comparisons are not significant ($P > .05$).

[a] Mean of paired differences = 7.5 years; SD = 8.5 years ($P = .00018$).

[b] Difference of means = 6.9 years; SD = 3.7 years ($P = .03$).

[c] Mean of paired differences = 5.7 years; SD = 9.7 years ($P = .0095$).

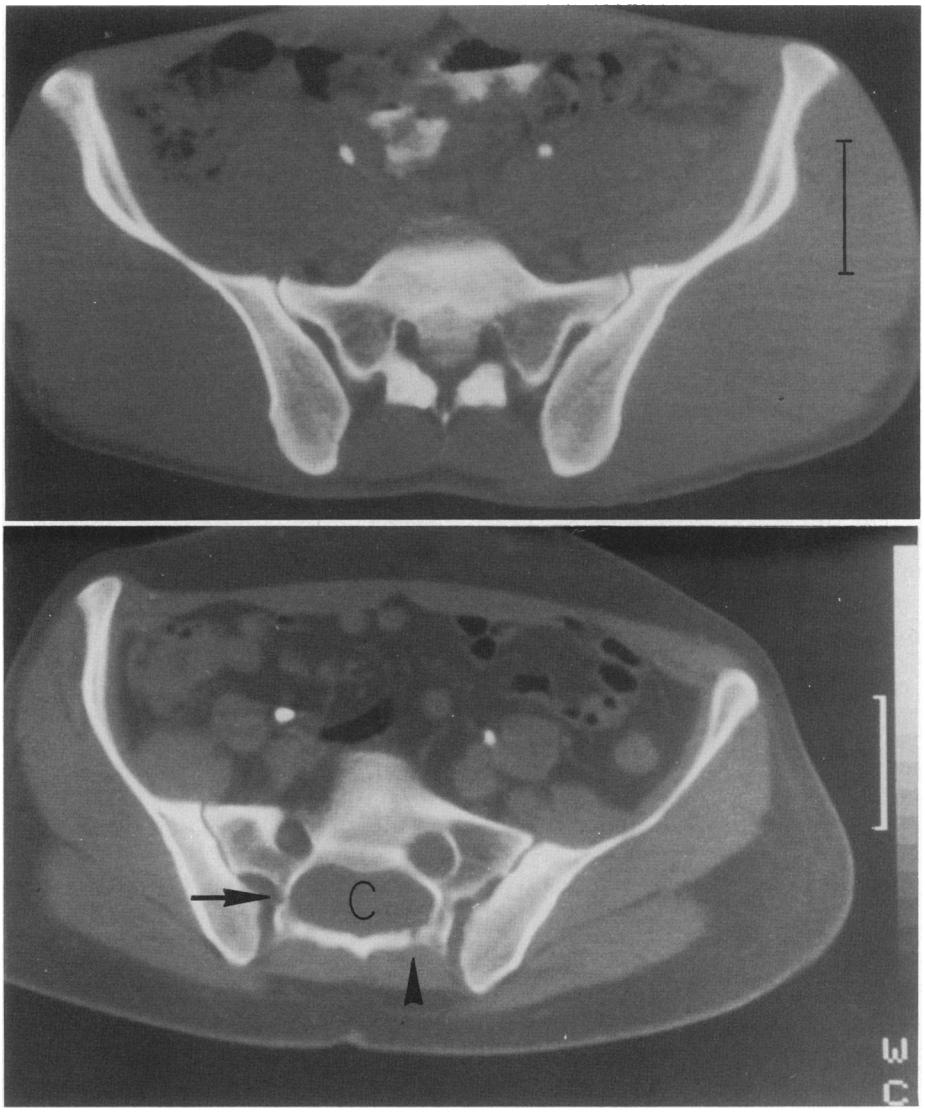

Figure 1 Computed tomogram of S1 in young adult men with the Marfan syndrome. *A*, No evidence of dural ectasia in a 26-year-old. **B**, The neural canal (C) is widened, and the pedicles (arrow) and laminae (arrowhead) are thinned in a 30-year-old. The bars indicate 5 cm in both cases.

dural ectasia was judged severe (fig. 2, 3). Both of the patients who had radicular pain in the legs or buttocks and objective neurologic signs of root compression had severe dural ectasia. Conversely, 11 of the patients with marked vertebral erosion or meningoceles had no neurologic signs or symptoms. Myelography, performed in the patients with radicular signs, excluded intervertebral disc herniation and confirmed that the pelvic masses communicated with the subarachnoid space (fig. 3*B*). None of the control patients without Marfan syndrome had evidence of dural ectasia.

Comparison of the interpretations of Marfan patients' CT scans made during the first session, when the radiologist was blind only to phenotypic severity and not diagnosis, with the interpretations made during the second session, when the radiologist was blind to whether the patient had the Marfan syndrome, showed no intraobserver variation in detection of dural ectasia.

Dural Ectasia and Phenotypic Severity

Figure 4 shows the distributions of severity scores for subjects in the present study. The mean scores of

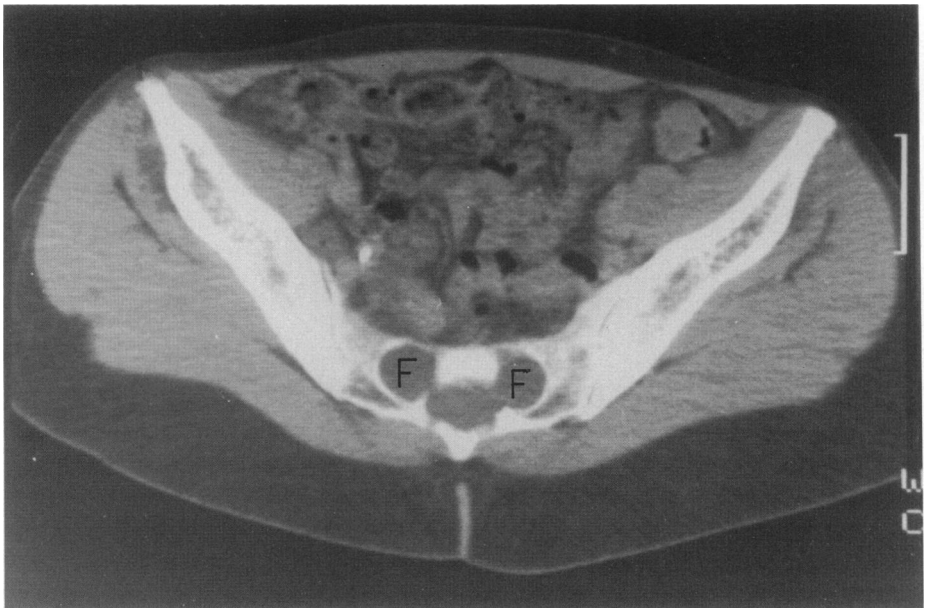

Figure 2 Computed tomogram at the S2-S3 level in a 27-year-old woman with the Marfan syndrome. The neural foramina (F) are markedly widened, and the cortex of the pedicles and laminae is eroded. The bar indicates 5 cm.

patients with dural ectasia, while higher than those of patients without dural ectasia, were not significantly so, and the distributions of scores showed considerable overlap. Examination of paired differences between subjects and age-matched controls who had not undergone CT showed significantly higher severity in both male and female subjects (table 1).

We examined the relationship between dural ectasia and several of the other pleiotropic features of the Marfan syndrome. We found no evidence of association between dural ectasia and (1) ectopia lentis (2) aortic dissection (3) scoliosis, or (4) joint laxity.

Discussion

In patients with the Marfan syndrome who underwent body CT evaluation primarily because of known or suspected severe aortic involvement, dural ectasia was a common finding. Of Marfan patients who had CT evaluation, those with dural ectasia were not distinguishable from those without it, on the basis of either overall severity of the Marfan phenotype or any single pleiotropic feature. Although we cannot make any strong statement about prevalence of dural ectasia in the Marfan syndrome in general, several facts suggest that the prevalence of about two-thirds that was found in our subjects is reasonably accurate. First, although most of the subjects were studied because of vascular problems, aortic complications, while not inevitable, are common enough in the Marfan syndrome that the patients likely do not differ substantially from the main (Murdoch et al. 1972). Nearly all of the age-matched control patients with the Marfan syndrome had some degree of aortic-root dilatation which had not progressed to the point of requiring surgery. Second, although the subjects who underwent CT had a distribution of severity scores higher than the control patients (fig. 4), the paired differences for both males and females were largely accounted for by aortic surgery, a fact worth 6 points on the severity score. Thus, while biased by process of selection, our subjects seem reasonably representative of people with the Marfan syndrome in general. Development of methods for detecting dural ectasia less invasively than by CT—methods such as magnetic resonance imaging—should in the future permit selection of subjects with less bias.

Dural ectasia may occur in von Recklinghausen neurofibromatosis and other heritable disorders of connective tissue, such as the Ehlers-Danlos syndromes (Mitchell et al. 1967; Feldman, 1988). In the general population, dural ectasia, arachnoid cysts, or pelvic meningoceles are rare occurrences and are usually associated with lesions that increase intrathecal pressure, trauma, or spinal surgery (Meschan and Coin 1985).

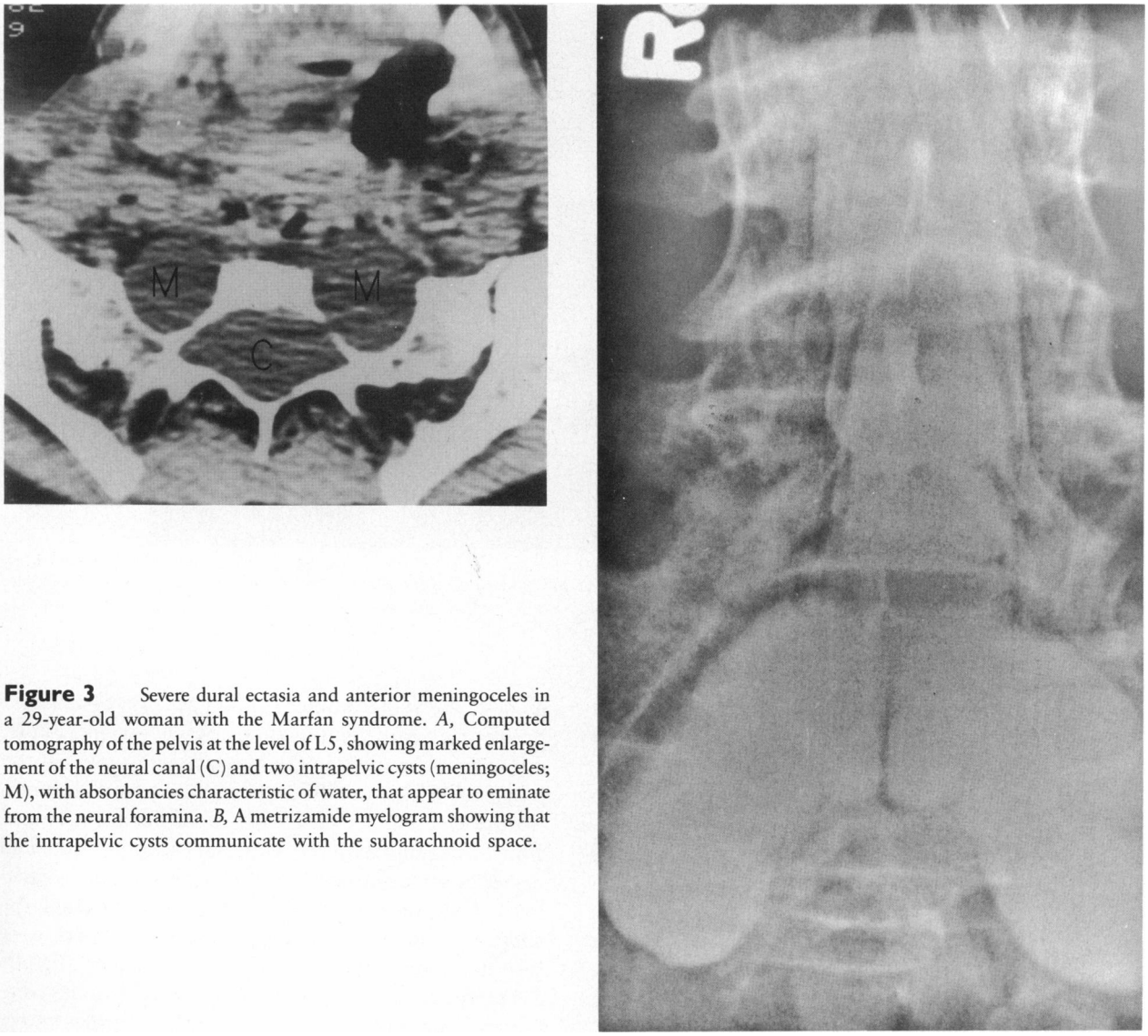

Figure 3 Severe dural ectasia and anterior meningoceles in a 29-year-old woman with the Marfan syndrome. *A,* Computed tomography of the pelvis at the level of L5, showing marked enlargement of the neural canal (C) and two intrapelvic cysts (meningoceles; M), with absorbancies characteristic of water, that appear to eminate from the neural foramina. *B,* A metrizamide myelogram showing that the intrapelvic cysts communicate with the subarachnoid space.

We found no suggestion of dural ectasia in the 57 age- and sex-matched non-Marfan control patients.

Dural ectasia, arachnoid cysts, anterior and posterior meningoceles, and other defects of lumbosacral vertebrae have been reported in fewer than 12 cases of the Marfan syndrome (Nelson 1958; Wilner and Finby 1963; Thierry et al. 1969; Strand and Eisenberg 1971; Wier 1973; Newman and Tilley 1979; Le Mercier et al. 1980; Cilluffo et al. 1981; Chu 1983). Reasons for detection have varied from serendipity to focused evaluations for neurologic signs, back pain, and pelvic masses. From these case reports and the series reported here, no strong association between severity of symptoms and anatomic changes emerges. Most patients with dural ectasia are not symptomatic.

The pathogenesis and natural history of the various anatomic changes that are now documented in the lower neuraxis of Marfan patients are unclear. Longitudinal studies, which could address both (*a*) whether meningoceles are congenital or develop after dural ectasia is established and (*b*) the rate of dilatation of the neural canal are needed. In these respects, the mean ages of patients with and without dural ectasia did not differ significantly, and no changes in dural ectasia occurred over time in 15 patients who had serial CT examinations 2–5 years apart. It is tempting to speculate that

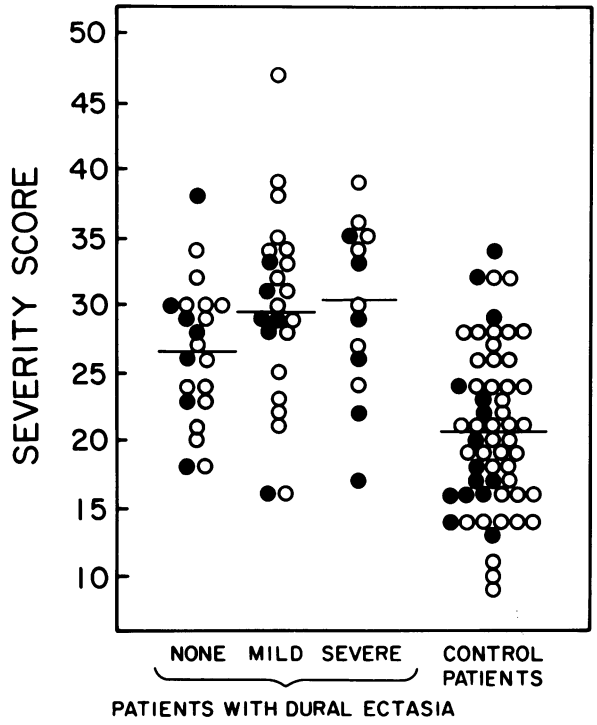

Figure 4 Distribution of phenotypic severity scores for subjects with no, mild, or severe dural ectasia and for age-matched control patients. Females are indicated by closed circles, and males are indicated by open circles; the horizontal bars indicate the mean severity score of each group.

dural ectasia arises from the continuous, and somewhat pulsatile, pressure of the cerebrospinal fluid on a connective-tissue membrane that is weakened by a defect of extracellular matrix. In upright posture, subarachnoid pressure is highest in the caudal neural canal, which would account for the predilection to lumbosacral vertebral erosions, arachnoid cysts, and pelvic meningoceles. The latter arise when the arachnoid protrudes through openings in the dura, such as occur normally at nerve roots.

Several patients with the Marfan syndrome (Chu 1983), including two of the subjects of the present study, have had a dilated cisterna magna and increased cerebrospinal fluid over the convexities of the brain, as detected by cranial CT. We did not examine routinely the neuraxis above the cervical region, and the frequency of intracranial changes due to dural ectasia in the Marfan syndrome remains unclear. However, whenever a patient with the Marfan syndrome develops neurologic symptoms or signs that could be attributed to any level of the neuraxis, the potential for dilated cerebrospinal fluid–filled areas of the subarachnoid space should be considered. Although we have not encountered difficulties with or adverse consequences of spinal anesthesia, the potential for dilution or pooling of intrathecal drugs should be considered. Because patients with the Marfan syndrome occasionally need surgery on the lower spine on account of spondylolisthesis or scoliosis, orthopedic surgeons should be aware of the potential complication of dural ectasia and diverticula. We know of one case (J. Graham, personal communication), in addition to the one reported in the literature (Le Mercier et al. 1980), in which an anterior meningocele was correctly diagnosed only after surgical exploration and incision of a "pelvic mass."

Genetic heterogeneity cannot be the only factor determining variable expression of dural ectasia. While three pairs of relatives were concordant for dural ectasia (a mother and daughter were affected, and two brothers and a brother and sister were not), another pair (first cousins) was discordant.

Acknowledgment

This work was supported in part by General Clinical Reserch Center grant RR 00722 from the National Institutes of Health.

References

Chu, N.-S. 1983. Marfan's syndrome and epilepsy: report of two cases and review of the literature. Epilepsia **24:** 49–55.

Cilluffo, J. M., M. R. Gomez, D. F. Reese, B. M. Onofrio, and R. H. Miller. 1981. Idiopathic ("congenital") spinal arachnoid diverticula. Mayo Clin. Proc. **56:**93–101.

Clericuzio C., C. Eberle, and M. Kornfeld. 1986. Minicore myopathy in two patients with the Marfan syndrome (abstract). Am. J. Med. Genet. **15:**724–725.

Feldman, F. 1988. Tuberous sclerosis, neurofibromatosis, and fibrous dysplasia. Pp. 4033–4072 *in* D. Resnick and G. Niwayama, eds. Diagnosis of bone and joint disorders. 2d ed. W. B. Saunders, Philadelphia.

Fishman, E. K., S. J. Zinreich, A. J. Kumar, A. E. Rosenbaum, and S. S. Siegelman. 1983. Sacral abnormalities in Marfan syndrome. J. Comput. Assist. Tomogr. **7:**851–856.

Gott, V. L., R. E. Pyeritz, G. J. Magovern, Jr., D. E. Cameron, and V. A. McKusick. 1986. Surgical treatment of aneurysm of the ascending aorta in the Marfan syndrome: results of composite-graft repair in 50 patients. N. Engl. J. Med. **314:**1070–1074.

Hall, J., R. E. Pyeritz, D. L. Dudgeon, and J. A. Haller, Jr. 1984. Pneumothorax in the Marfan syndrome: prevalence and therapy. Ann. Thorac. Surg. **37:**500–504.

Le Mercier, Y., J. M. Decazes, D. Mechali, A. Redondo, J.

Aboulker, and J. P. Coulaud. 1980. Meningite purulente par inoculation chirurgical d'un méningocele sacrée antérieure. Ann. Med. Interne (Paris) **131**:289–290.

McKusick, V. A. 1972. The Marfan syndrome. Pp. 61–223 *in* V. A. McKusick. Heritable disorders of connective tissue. C. V. Mosby, St. Louis.

Meschan, I., and C. G. Colin. 1985. Computed tomography of the spine. Pp. 135–190 *in* I. Meschan and R. M. Farrer-Meschan, eds. Roentgen signs in diagnostic imaging. Vol. 3. Spine and central nervous system. W. B. Saunders, Philadelphia.

Mitchell, G. E., H. Lourie, and A. S. Berne. 1967. The various causes of scalloped vertebrae with notes on their pathogenesis. Radiology **89**:67–74.

Murdoch, J. L., B. A. Walker, B. L. Halpern, J. W. Kuzma, and V. A. McKusick. 1972. Life expectancy and causes of death in the Marfan syndrome. N. Engl. J. Med. **286**: 804–808.

Nelson, J. D. 1958. The Marfan's syndrome, with special reference to congenital enlargement of the spinal canal. Br. J. Radiol. **31**:561–564.

Newman, P. K., and P. J. B. Tilley. 1979. Myelopathy in Marfan's syndrome. J. Neurol. Neurosurg. Psychiatry. **42**:176–178.

Pages, M., B. Echenne, A.-M. Pages, A. Dimeglio, and A. Sires. 1985. Multicore disease and Marfan's syndrome: a case report. Eur. Neurol. **24**:170–175.

Pyeritz, R. E. 1986. The diagnosis and management of the Marfan syndrome. Am. Fam. Physician **34**:83–94.

Pyeritz, R. E., and V. A. McKusick. 1979. The Marfan syndrome—diagnosis and management. N. Engl. J. Med. **300**:772–777.

Strand, R. D., and H. M. Eisenberg. 1971. Anterior sacral meningocele in association with Marfan's syndrome. Radiology **99**:653–654.

Streeten, E. A ., E. A. Murphy, and R. E. Pyeritz. 1987. Pulmonary function in the Marfan syndrome. Chest **91**: 408–412.

Thierry, A., J.-P. Archimbaud, G. Fischer, M. Friedel, and L. Mansuy. 1969. La Méningocele sacrée antérieure. Neurochirurgie **15**:389–412.

Weit, B. 1973. Leptomeningeal cysts in congenital ectopia lentis. J. Neurosurg. **38**:650–654.

Wilner, H. I., and N. Finby. 1963. Skeletal manifestation in the Marfan syndrome. JAMA **187**:490–495.