The Spine Journal 19 (2019) 1412–1421

Clinical Study

Dural ectasia in Marfan syndrome and other hereditary connective tissue disorders: a 10-year follow-up study

Tordis Böker, MD[a,b,*], Thy Thy Vanem, MD[a,c], Are Hugo Pripp, PhD[d], Svend Rand-Hendriksen, MD, PhD[e], Benedicte Paus, MD, PhD[a,f], Hans-Jørgen Smith, MD, PhD[a], Rigmor Lundby, MD, PhD[a,b]

[a] *Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway*
[b] *Department of Radiology and Nuclear Medicine, Oslo University Hospital, Ullevål, PO BOX 4956 Nydalen, Oslo 0424, Norway*
[c] *Department of Cardiothoracic Surgery, Oslo University Hospital, Oslo, Norway*
[d] *Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway*
[e] *TRS, National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway*
[f] *Department of Medical Genetics, Oslo University Hospital, Oslo, Norway*
Received 28 January 2019; revised 11 April 2019; accepted 11 April 2019

Abstract

BACKGROUND CONTEXT: Dural ectasia is widening of the dural sac often seen in patients with Marfan syndrome and other hereditary connective tissue disorders. Dural ectasia can cause specific symptoms and is associated with surgical complications. The knowledge on how and at which age dural ectasia develops is incomplete. There is no established gold standard for diagnosing dural ectasia, making it difficult to compare results from different studies.

PURPOSE: Our primary aim was to explore whether the radiological findings of dural ectasia changed after 10 years in an adult cohort with suspected Marfan syndrome. Our secondary aim was to re-evaluate the radiological criteria of dural ectasia.

STUDY DESIGN: Prospective cohort study.

PATIENT SAMPLE: Sixty-two persons from a cross-sectional study of 105 persons with suspected Marfan syndrome were included in a 10-year follow-up of dural ectasia. Forty-six were diagnosed with Marfan syndrome, 7 with Loeys-Dietz syndrome, and 5 with other hereditary connective tissue disorders. For comparison 64 matched hospital controls were evaluated.

OUTCOME MEASURES: Previously used radiological criteria for dural ectasia based on quantitative measurements of the lumbosacral spine.

METHODS: MRI of the lumbosacral spine was performed if not contraindicated, and if so then CT was performed. Differences in the study group between baseline and follow-up were assessed with paired Student *t* test, Wilcoxon rank signed test, and McNemar test. Receiver operating characteristic curves were constructed to assess the ability of radiological measurement to differentiate between the study and control group.

RESULTS: Fifty-two of 58 patients with hereditary connective tissue disorders and 11 controls had dural ectasia at follow-up. Forty-five Marfan patients had dural ectasia at follow-up vs. 41 at baseline. Five Loeys-Dietz patients had dural ectasia at follow-up vs. four at baseline. Twenty-four Marfan and 2 Loeys-Dietz patients had anterior sacral meningocele at follow-up, compared with 21 and 1, respectively, at baseline. Three Marfan patients developed herniation of a nerve root sleeve during follow-up.

FDA device/drug status: Not applicable.

Author disclosures: ***TB:*** Grant: Ødegaards and Frimann-Dahls Foundation to Promote Norwegian Radiological Research (B). ***TTV:*** Nothing to disclose. ***AHP:*** Nothing to disclose. ***SR-H:*** Nothing to disclose. ***BP:*** Nothing to disclose. ***H-JS:*** Nothing to disclose. ***RL:*** Grants: Ødegaards and Frimann-Dahls Foundation to Promote Norwegian Radiological Research (B); Oslo University Hospital, Department of Radiology and Nuclear Medicine, Science Found (B); Roy Magnus Løkens Foundation (D). Support for travel to meetings for the study or other purposes: Halls Heart Foundation (B).

Funding: This study was supported by funds from Roy Magnus Løkens Foundation for Medical Imaging, Oslo University Hospital, Department of Radiology and Nuclear Medicine, Science Found and The Norwegian Society of Medical Radiology.

* Corresponding author. Department of Radiology and Nuclear Medicine, Oslo University Hospital, Ullevål, PO BOX 4956 Nydalen, 0424 Oslo, Norway. Tel.: +47 22 11 93 50; fax: +47 22 11 93 66.

E-mail addresses: tordis.boker@medisin.uio.no, tordisbok@yahoo.no (T. Böker).

https://doi.org/10.1016/j.spinee.2019.04.010

This was not seen in other individuals. The dural sac ended significantly lower at follow-up, and the dural sac ratio at level L5 was significantly increased from baseline in the Marfan patients.
CONCLUSIONS: In Marfan and Loeys-Dietz syndrome, dural ectasia may present or worsen during adulthood. The cut-off value of dural sac ratio at level S1 is suggested elevated to 0.64. The results from the present study may help as guidance for appropriate follow-up of patients with dural ectasia.

Keywords: Spine; Dural ectasia; Anterior sacral meningocele; Marfan syndrome; Loeys-Dietz syndrome; Hereditary connective tissue disorders; MRI; CT

Introduction

Throughout the last decades, several different hereditary connective tissue disorders (HCTD) have been described, and a broad spectrum of genes have been identified in which mutations cause HCTD [1]. Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and Ehlers-Danlos syndrome are three out of many HCTD that share clinical features, and dural ectasia (DE) is a common finding in all three syndromes [2]. DE is widening of the dural sac or spinal nerve root sleeves, usually associated with bony erosions of the posterior vertebral body [3]. There is lack of knowledge on how and at which age DE develops in patients with HCTD, and no unified gold standard for diagnosing abnormal widening of the dural sac has been established.

MFS is an autosomal dominant connective tissue disorder that affects multiple organ systems such as the heart, blood vessels, lungs, muscles, skeleton, eyes, and integument. The prevalence is estimated to be 1.5 to 17.2 per 100,000 [4,5]. More than 1,800 different disease-causing mutations are found in fibrillin-1 *(FBN1)* according to the UMD-FBN1 mutations database [6]. The expressivity of MFS shows great variation, even among relatives with the same known disease-causing mutation [7,8].

So far, most attention has been given to the cardiovascular manifestations as they are associated with high morbidity and mortality if undetected or not properly treated. A common cardiovascular feature is dilation of aorta which can lead to aortic dissection and risk of aortic rupture [7,9].

The prevalence of DE in adults diagnosed with MFS varies according to the chosen method for dural assessment [10]. In a study of DE in 150 patients with a mutation in *FBN1* [10], the prevalence of DE was 89% with the criteria of Oosterhof [11] and Habermann [12], 83% with Fattori [13], 78% with Lundby [14], and 59% with Ahn [15]. Few studies have followed groups of MFS patients for a longer period, and to our knowledge only one report is published on a MFS cohort examined for DE 10 years after the first examination [16]. DE is said to cause chronic lower back pain and radiculopathy [17−19], and DE is associated with postural headache related to spontaneous spinal cerebrospinal fluid leaks [20−23]. Complications of DE are reported to comprise fixation failure during spine deformity corrective surgery [24] and inadequate spinal anesthesia [25,26]. That anterior sacral meningoceles can mimic ovarian cysts is also a potential cause of complications [27−29].

In the study presented in this paper, we performed a 10-year follow-up in 2014 to 2015 based on the cohort first examined in 2003 to 2004, using the same method as at baseline [14]. The assessment of DE was based on the presence of at least one of the following four findings: (1) anterior sacral meningocele (AM), (2) herniation of one or more of the nerve root sleeves, (3) dural sac diameter (DSD) at S1 or inferior>DSD at level L4, and (4) dural sac ratio (DSR) at S1≥0.59.

The primary aim of our study was to gain new information on how DE develops in adults with MFS by re-investigating the morphology of the lumbosacral spine. We hypothesized that DE may increase during a time span of 10 years. Our secondary aim was to re-evaluate the diagnostic criteria of DE, by analyzing the DSR cut-off value.

Materials and methods

The follow-up study was approved by the Regional committees for Medical and Health Research Ethics, South East, Norway, registration number 2013/2109. All participants gave their informed consent. All the participants were 18 years or older when included at baseline.

Study population

In 2003 to 2004, 105 adults (≥18 years) with presumed MFS were recruited to a Norwegian cross-sectional study on MFS [30]. At baseline, a case-control study of the prevalence of DE and characteristics of the lower lumbar and sacral spine were carried out [14]. In 2014 to 2015, a 10-year follow-up study of the prevalence of DE and characteristics of the lower lumbar spine were performed. Eighteen of the 105 participants recruited in 2003 to 2004 had died before the end of inclusion at follow-up in December 2015. Of the 87 survivors, 62 individuals gave their informed consent for participation, 42 women; mean age 49.2±12.5, range 31 to 80 years and 20 men; mean age 44.0±8.9 years, range 30 to 65 years. Two patients had at baseline undergone fixation of the spine due to scoliosis, one was reoperated during the follow-up period. Two patients underwent

fixation of the spine during the follow-up, one due to scoliosis, the other due to listhesis. The surgery was not considered to affect dura. Four persons from the study group of 62 were excluded from further analyses, because of no clinical or molecular indication of HCTD. The diagnoses of the 58 study patients were reassessed in 2016, based on clinical features and genetic testing. According to the reassessment 46 had MFS [2], 7 LDS (1 LDS1, 5 LDS2, and 1 LDS3), 1 congenital contractural arachnodactyly, 3 hypermobile Ehlers-Danlos syndrome, and 1 familial ectopia lentis. Only the MFS and LDS patients were analyzed statistically due to low numbers of patients diagnosed with other HCTD. For the other diagnoses, the results are shown as counts in Table 2.

Control population

A new control group was found for the 10-year follow-up study. As in the primary case-control study of DE in MFS [14], the controls were chosen from the pool of patients in the PACS at our institution by reviewing patients screened for metastases or multiple sclerosis 2006 to 2016. The selected cases were sorted after examination date, and the candidates were collected according to the following criteria: sex- and age-matched individuals asymptomatic with respect to the lumbosacral spine and without any known HCTD or compression fractures. With few exceptions, the controls were within 5 years of age of the study patients, and the mean and the median age matched the study group.

The control group included 64 individuals, 37 women; mean age 44.8±10.2 years, range 30 to 72 years, and 27 men; mean age 44.7±12.3 years, range 20 to 68 years.

Imaging of the study group

A 1.5 T MRI of the lumbosacral spine was performed unless contraindicated, then CT was obtained. Of the 62 study patients, 59 had MRI at baseline and/or at 10-year follow-up; of these 49 had MRI at both occasions, 57 had MRI at baseline and 51 at 10-year follow-up. MRI of the study patients was performed with a 1.5 T unit (Magnetom Avanto, Siemens, Erlangen, Germany). The imaging protocol included sagittal T1-weighted (TE/TR=10/474) and T2-weighted (TE/TR=84/2,300) turbo spin echo sequences with slice thickness 4 mm. T2-weighted sequences were also obtained in the coronal plane and in axial planes angulated parallel to the three lower lumbar intervertebral discs.

CT investigations were performed with a Somatom Sensation 16 scanner (Siemens, Erlangen Germany). Axial, sagittal, and coronal MPR reconstructions with 5 mm slice thickness were obtained.

Imaging of the control group

MRI of the controls was performed at different 1.5 T MR units at our institution with sagittal T1- and T2-weighted turbo spin echo sequences.

Measurements and definitions

For each subject, the diagnosis of DE was defined as presence of one or more of the following four findings: AM, one or more dural sac nerve root sleeve herniations, DSD at level S1 or inferior (DSD sacrum)>DSD at level L4 and DSR at S1≥0.59. These are the same criteria used for establishing the DE diagnosis in the case-control study at baseline [14]. AM was defined as a herniation of the dural sac through a defect in the anterior surface of the sacrum or when the sacral meninges were herniating anteriorly into the pelvis through an expanded foramen [31]. Herniation of a nerve root sleeve, a lateral meningocele, was defined as a wide nerve root sleeve throughout the intervertebral foramen ending in a pouch. Lumbosacral anteroposterior vertebral body diameter was measured at levels L3 through S1. The measurements were done halfway between the superior and inferior endplates and perpendicularly to the long axis of the vertebral body. DSD were measured from level T12 to the inferior end of the dural sac. The measurements were done halfway between the superior and inferior endplates and perpendicularly to the long axis of the spinal canal. All the measurements were obtained in the midsagittal plane. DSRs were calculated as quotients of the DSD to the anteroposterior vertebral body diameter (VBD) halfway between the superior and inferior endplates at levels L3−S1, (DSR=DSD/VBD). Presence of DSD at level S1 or inferior greater than DSD at level L4 was noted.

AM and nerve root sleeve herniations were assessed with respect to presence and increase in size. The endpoint of the dural sac was registered.

All measurements of the study patients at baseline were performed in Sectra PACS, version IDS5. All measurements of the controls at baseline were done in Agfa PACS (unknown version). All measurements at 10-year follow-up were done in Sectra PACS, version 18.1.1 IDS7.

Evaluation

All imaging studies at 10-year follow-up were evaluated by one musculoskeletal radiologist (TB) and one neuroradiologist (RL) in consensus. Both readers were unaware of the clinical status of the study patients but not blinded to which group (study or control) the patients belonged.

Statistical analysis

Continuous data were described as mean, standard deviation, and range (ie, minimum-maximum), and categorical data were described as number of observations and percentage. Differences in the study group between baseline and follow-up were assessed with paired Student *t* test for continuous data, Wilcoxon rank signed test for discrete data, and McNemar test for categorical data. Differences in the two control groups were assessed with independent *t* test for continuous data, Mann-Whitney *U* test for discrete data, and chi-square test for categorical data. A scatterplot was

made to illustrate association between radiological measurements in the study and control group in comparison with age. Receiver operating characteristic (ROC) curves were constructed to assess the ability of radiological measurement to differentiate between the study and control group. Cut-off values with given sensitivity and specificity were derived from the ROC curves.

All statistical analyses were performed by using the Statistical Package for the Social Sciences, Version 24.0 (IBM SPSS Statistics).

Results

To compare measurements done in the former and the present PACS, the measurements were repeated in the new PACS in 20 of the study patients who had MRI at baseline. There was a small but significant change in some of the absolute measurements between the two systems. There were however no significant differences in ratios.

The characteristics and measurements in the patient groups and controls at baseline and follow-up are shown in Table 1.

Mean changes in DSR from baseline to follow-up were analyzed for levels L3–S1. At level L5, there was a significant increase of 0.028 (p=.02) in the MFS patients.

The relationships between DSR L5 and age in patients with MFS and in controls are shown in Fig. 1.

The inferior end of the dural sac had a significantly lower position at follow-up compared with baseline in MFS patients. Only MFS patients had dural sacs ending inferior to S3, but the number of patients with dural sac ending inferior to S3 was unchanged. Few controls had dural sac ending lower than S2.

Findings pertinent to the diagnosis of DE are shown in Table 2.

Only patients diagnosed with MFS and LDS had AM. During the 10-year follow-up period, eight of the MFS patients developed AM, or had increased size of their AM (p=.005; Fig. 2).

Only MFS patients developed herniation of one or more nerve root sleeves during the follow-up period (Fig. 3), but there was no significant difference from baseline. In the control group at baseline, one individual had herniation of

Table 1
Characteristics of patients with MFS, patients with LDS, and controls at baseline and follow up

Characteristics	MFS N=46 33 (72%)			LDS N=7 4 (57%)		Controls Controls B N=101 64 (63%)	Controls Controls F N=64 37 (58%)		HCTD compared with Controls F
Females N (%)	Baseline	Follow-up	p	Baseline	Follow-up	Baseline	Follow-up	p	p
Age									
mean±SD	39.3±11.8	50.1±11.5		30.1±9.0	40.9±9.1	39.6±12.9	44.8±11.1		
Median	38.0	49.5		29.0	41.0	40.0	44.0		
DSR L3									
mean±SD	0.50±0.11 (2)	0.51±0.11 (1)		0.44±0.06	0.46±0.10	0.46±0.07	0.41±0.07		
mean difference*	0.00007		.995	0.1757		−0.04640		<.001	<.001
95% CI	(−0.023–0.023)		N=43	(−0.043–0.078)		(−0.069 to −0.024)			
DSR L4									
mean±SD	0.49±0.10 (3)	0.51±0.11 (1)		0.42±0.06	0.45±0.08	0.43±0.07	0.40±0.07		
mean difference*	0.01751		.087	0.02986		−0.03320		.004	<.001
95% CI	(−0.003–0.038)		N=43	(−0.005 to 0.065)		(−0.056 to −0.011)			
DSR L5									
mean±SD	0.59±0.16 (4)	0.62±0.15 (1)		0.42±0.11	0.47±0.11	0.42±0.08	0.40±0.07		
mean difference*	0.02777		.019	0.05040		−0.02055		.102	<.001
95% CI	(0.005–0.051)		N=42	(−0.020 to 0.121)		(−0.045 to 0.004)			
DSR S1									
mean±SD	1.02±0.81 (6)	0.99±0.40 (2)		0.58±0.24 (2)	0.59±0.23	0.41±0.13 (5)	0.46±0.11 (1)		
mean difference*	−0.05365		.596	0.09674		0.04715		.021	<.001
95% CI	(−0.257 to 0.149)		N=40	(−0.008 to 0.202)		(0.007–0.087)			
Inferior end DS	(2)	(1)	0.046						
S1	4 (8.7%)	3 (6.5%)		2 (28.6%)	2 (28.6%)	22 (21.8%)	13 (20.3%)		
S2	21 (45.7%)	20 (43.5%)		2 (28.6%)	0 (0%)	68 (67.3%)	46 (71.9%)		
S3	11 (23.9%)	14 (30.4%)		3 (49.9%)	5 (71.4%)	11 (10.9%)	4 (6.3%)		
S4	6 (13%)	6 (13%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		
S5	2 (4.3%)	2 (4.3%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)		

HCTD = hereditary connective tissue disorders; MFS = Marfan syndrome; LDS = Loeys-Dietz syndrome. B = baseline; F = follow-up; p = p value; DS = dural sac; DSR = dural sac ratio.

Whole numbers in parentheses: missing cases, not given if no missing cases.

* mean difference=Follow up−baseline.

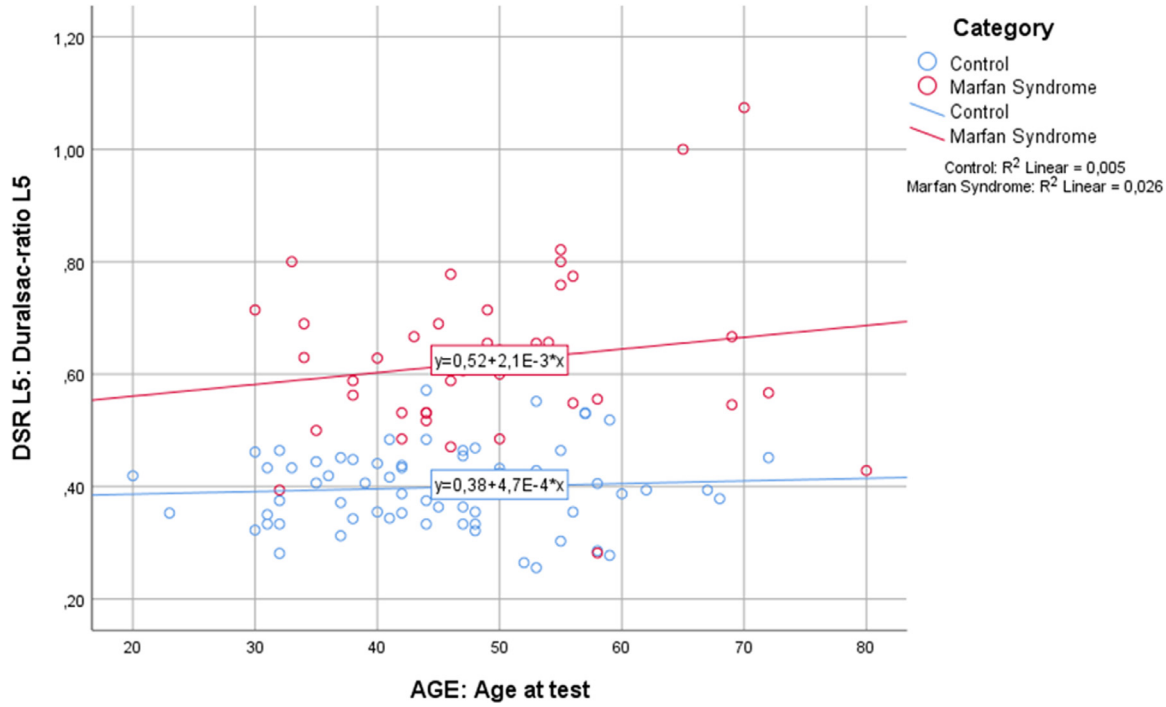

Fig. 1. Relationship between age and DSR at level L5 in patients with MFS and in controls.

nerve root sleeves; none of the controls in the follow-up had this finding.

There was no significant increase in the number of patients with DSD sacrum>DSD L4 and no significant difference between the two control groups.

Compared with baseline, DSR S1≥0.59 was present in more MFS and LDS patients at follow-up, but the increase in numbers was not significant. For this finding, there was no significant difference between the controls at baseline and the controls at follow-up.

Based on the criteria for DE recommended by Lundby et al. [14], there was an increase in the number of patients diagnosed with DE at follow-up, but the change was not significant. According to the same criteria, 12.9% of the controls in the baseline study and 17.2% of the controls in the follow-up study had DE.

In all the controls, except one at baseline who had herniation of a nerve root sleeve, the diagnosis of DE was dependent on either DSD S1>DSD L4 or DSR S1≥0.59. To evaluate the discriminative ability of DSR, an ROC analysis of DSR L3−S1, comparing MFS patients and controls at follow-up, was performed (Fig. 4). The best results were obtained for DSR L5 (area under the curve (AUC) 0.93) and DSR S1 (AUC 0.94).

Discussion

The results of the present study support the finding of Sheikhzadeh et al., who concluded that DE is frequent in patients with *FBN1* mutations irrespective of age [10]. In the previous diagnostic criteria for MFS from 1996 [32], DE counted as a major criterion, but in the revised criteria from 2010 less emphasize is put on DE [2]. Accordingly, Sheikhzadeh et al. concluded from their study of 150 *FBN1* mutation positive patients that DE showed an impact on the final diagnosis of MFS only when the previous diagnostic criteria for MFS from 1996, and not the revised criteria were applied.

Although not significant, we found that DE may appear in adulthood, implying an age-dependent penetrance of the feature (Fig. 1). Four out of 46 (p=.125) MFS patients and 1 out of 7 (p=1.00) LDS patients developed DE during the 10-year follow-up period (Table 2), supporting the conclusion from Sheikhzadeh's study that individuals diagnosed with *FBN1* mutations can develop increased widening of the lower dural sac as well as documenting the same event in LDS.

The results of the present study also support the finding of Sheikhzadeh et al. that the severity of DE in patients with *FBN1* mutations may increase with age (Fig. 1). In the only follow-up study of DE in patients with MFS, we have found in the literature, by Mesfin et al., no progression of DE was observed 10 years after the first examination [16]. The differences in the findings in our study compared with Mesfin et al. may be explained by a larger cohort with a wider age span in our study. While all MFS patients in our cohort had a mutation in *FBN1*, the patients' mutational status was not reported in the study by Mesfin et al.

While observing a nonsignificant increase in the number of MFS patients having DE during the 10-year follow-up period, a significant increase in the number that developed or had increased size of their AM was found. We found that three of the MFS patients developed AM and five had an

Table 2
Prevalence of enlarged dural sac signs at baseline and follow-up in patients and controls

	Hereditary connective tissue disorders N=58															Control groups			
	MFS n=46			LDS1 n=1		LDS2 n=5		LDS3 n=1		hEDS n=3		CCA n=1		EL n=1		Controls B n=101	Controls F n=64	Controls compared
Criteria	Baseline	Follow-up	p	B	F	B	F	B	F	B	F	B	F	B	F	Baseline	Follow-up	p
Ant. meningocele	21; 45.7%	24; 52.2%	.250	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1.000
Herniation≥1 n.r.s.	35; 76.1%	38; 82.6%	.453	1	1	2	2	1	1	1	1	0	0	0	0	1; 1.0%	0	.426
DSD sacr.>DSD L4	25 (3); 54.3%	26 (1); 56.5%	1.000	1	0	0	1	1	1	1	1	0	0	1	1	5; 5.0%	5; 7.8%	.454
DSR S1≥0.59	34 (6); 73.9%	41 (2); 89.1%	.250	1	1	0	3	0	1	0	0	0	0	1	0	10; 9.9%	8; 12.5%	.334
DSR S1≥0.72	27 (6); 58.7%	33 (2); 71.7%	.625	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1.000
DSR S1≥0.64	34 (6); 73.9%	37 (2); 80.4%	1.000	1	1	0	0	0	0	0	0	0	0	1	0	4; 4%	3; 4.7%	.821
DE Lundby criteria DSR≥0.59	41; 89.1%	45; 97.8%	.125	1	1	2	3	1	1	1	1	0	0	1	1	13; 12.9%	11; 17.2%	.339
DE Lundby criteria DSR S1≥0.72*	39; 84.8%	43; 93.5%	.125	1	1	2	2	1	1	1	1	0	0	1	1	6; 5.9%	5; 7.8%	.640
DE Lundby criteria DSR S1≥0.64†	41; 89.1%	43; 93.5%	1.000	1	1	2	2	1	1	1	1	0	0	1	1	8; 8.9%	7; 10.9%	.668

MFS, Marfan syndrome; LDS1, Loeys-Dietz syndrome type 1; LDS2, Loeys-Dietz syndrome type 2; LDS3, Loeys-Dietz syndrome type 3; hEDS, Ehlers-Danlos syndrome hypermobile type; CCA, congenital contractural arachnodactyly; EL, familial ectopia lentis; B, baseline; F, follow-up; p, p value; n.r.s.: nerve root sleeve.

Whole numbers in parentheses: missing cases, not given if no missing cases.

* Dural ectasia according to Lundby criteria but with DSRS1≥0.72.

† Dural ectasia according to Lundby criteria but with DSRS1≥0.64.

increased size of their AM, which is a significant change (p=.005). To our knowledge, this has not been described in a follow-up study previously. This finding supports the theory that DE can evolve into a more severe form during adulthood [10]. AM is a pathologic finding that may be a presentation of grave DE. AM has not been reported in a normal population [14,33], which is in line with no findings of AM in the control group in the present study. We consider AM to be relatively specific for HCTD, but AM can also be found in other conditions such as Currarino syndrome, neurofibromatosis type I, and ankylosing spondylodiscitis [34–37]. Further, all patients who developed an AM fulfilled other criteria for DE both at follow-up and at baseline. The findings support the theory that cerebrospinal fluid pressure in the lower end of the dural sac may cause erosions in the sacrum over time [12,38]. AM was only found in MFS and LDS patients in our study, which may imply that these patients have graver DE than patients with other HCTD.

There was no significant change in the number of patients with herniation of a nerve root sleeve or DSR S1≥0.59. An interesting observation is that the changes in these two parameters gave rise to the DE diagnosis in the patients who developed DE during the 10-year period.

For DSR L5, there was a significant increase from baseline to follow-up in the MFS patients; this finding supports the hypothesis that dural ectasia can develop in adulthood. Our findings in DSR S1 might be interpreted as inconsistent with the findings in DSR L5, as there was no significant change of DSR S1 in our cohort, but the DSR S1 was significantly higher in the MFS patients at both baseline and follow-up compared with the control groups. The significant difference between the two control groups at this level reflects that these are independent groups.

Even though only few patients (n=8) had dural sacs ending inferior to level S3, and no change in this number was observed, the finding is interesting as only MFS patients with DE were found to have dural sac endings inferior to S3. This might be a specific, although not very sensitive indication of DE in MFS. As far as we know, this has not been reported in a normal population [14,33].

No uniform consensus regarding imaging method, criteria, and cut-off values for diagnosing DE has been established [11–15,33,39]. In the present study, we found that the number of individuals diagnosed with DE varied according to the cut-off value used for DSR S1 (Table 2). With Oosterhof's criteria (DSR L5>0.48 and DSR S1>0.57) approximately 30% of the controls both at baseline and at follow-up would have been diagnosed with DE. Oosterhof's cut-off values for DSR L5 and S1 have previously been discussed by Lundby [14] and Pierro [33], both concluded that Oosterhof's method would give a too high proportion of a normal population the diagnosis of DE. Based on their findings in a cohort of 604 adults without symptoms from the lumbosacral spine, Pierro et al. concluded that the cut-off value for DSR at S1 used by Lundby

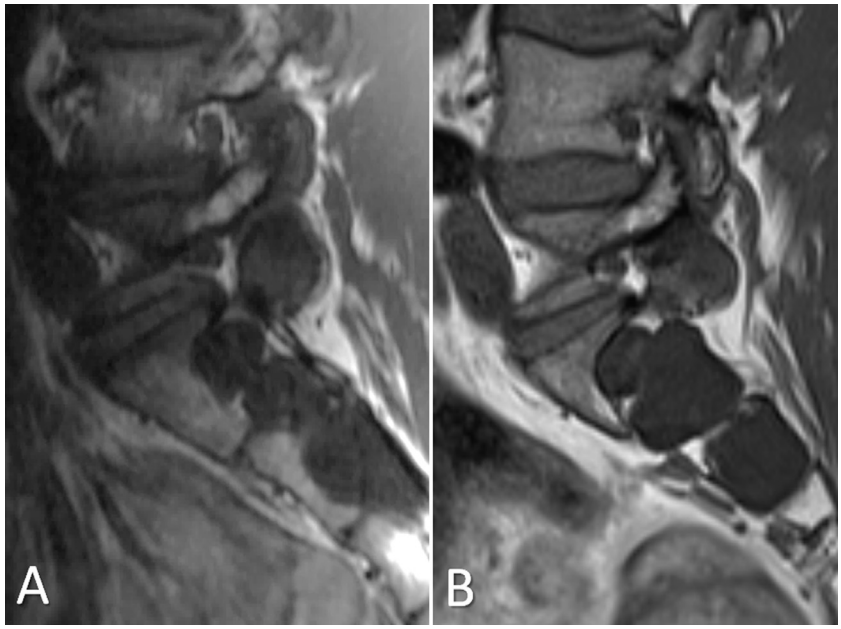

Fig. 2. MRI of a male patient with MFS, 19 years old at baseline, who has developed an anterior sacral meningocele. (Left) sagittal T1 at baseline. Dural ectasia without anterior sacral meningocele. (Right) sagittal T1 at follow-up. Dura is crossing the anterior sacral cortex consistent with anterior sacral meningocele.

et al., 0.59, was too low and suggested to increase it to 0.72 [33]. When the cut-off value for DSR at S1 was changed to 0.72 in our study, this gave a significant reduction in controls diagnosed with DE. No controls in our study had DSR S1≥0.72, and the ones who still had DE with this cut-off value (six and five at baseline and follow-up, respectively), were diagnosed based on other criteria, either herniation of one or more of the nerve root sleeves or DSD at S1 or inferior>DSD at level L4. Significantly fewer MFS patients reached the cut-off value of DSR S1≥0.72 compared with 0.59 both at baseline (seven, p=.016) and follow-up (eight, p=.008), which resulted in loss of the DE diagnosis in two MFS patients at baseline and two MFS patients and one LDS patient at follow-up. Although a cut-off value of 0.72 increases the specificity, it seems to reduce the sensitivity for the diagnosis of DE. The optimum cut-off value may be suggested by our ROC analysis (Fig. 4). The best discrimination between MFS patients and controls was found for DSR S1, and a cut-off value of 0.64 yielded the best combination of sensitivity and specificity, with a sensitivity of 84% and a specificity of 95%. Introducing this cut-off value in our study resulted in no loss of the DE diagnosis at baseline, but two MFS patients and one LDS patient lost this diagnosis at follow-up compared with the results with a cut-off value of 0.59. With the cut-off value of 0.64, 89.1% and 93.5% of the MFS patients were diagnosed with DE at baseline and follow-up, respectively, while 8.9% and 10.9% in the two control groups received this diagnosis. Hence, there was no significant increase in controls having DE compared with a cut-off value of 0.72 or significant

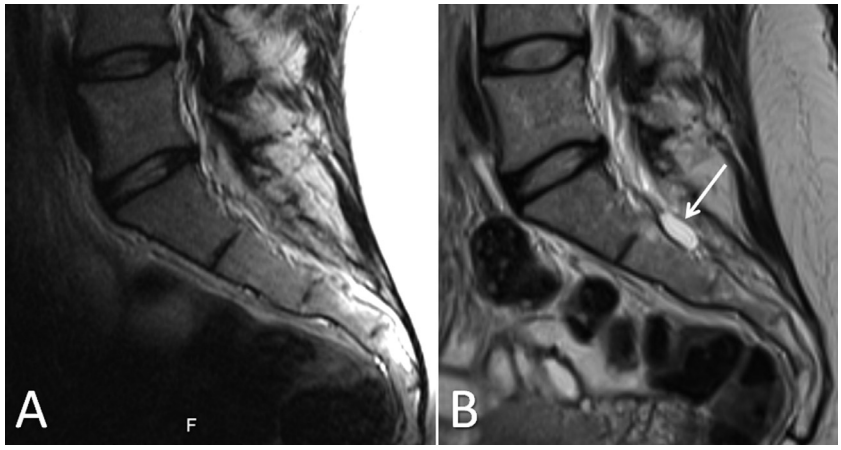

Fig. 3. MRI of a female patient with MFS, 20 years old at baseline, who has developed herniation of a nerve root sleeve. (Left) sagittal T2 at baseline. No herniation seen. (Right) sagittal T2 at follow-up. A nerve root sleeve herniation has become evident (arrow).

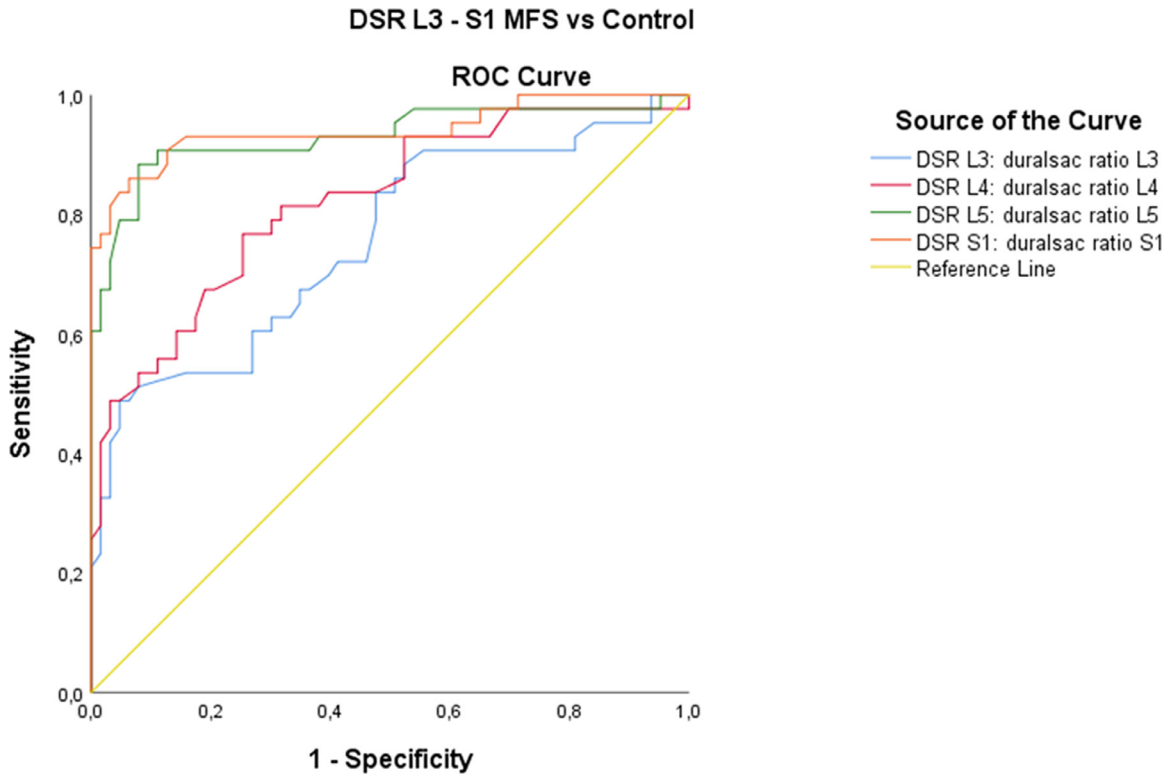

Fig. 4. ROC analysis of DSR at levels L3–S1 for MFS patients and controls at follow-up. The best discrimination between MFS patients and controls is found at levels L5 (AUC=0.93) and S1 (AUC=0.94).

decrease compared with a cut-off value of 0.59. A threshold value of 0.64 therefore seems like a reasonable compromise between sensitivity and specificity. Even though we know that very few patients rely on the finding of DE for their MFS diagnosis, in individual cases, it might be unfortunate to delay the diagnosis of DE by choosing a cut-off value for DSR as high as 0.72.

There are some limitations to our study. Our baseline cohort with suspected MFS turned out to have various HCTD, but only the MFS group was large enough to allow definite conclusions with respect to changes during the 10-year period. The second largest group, LDS, was small and consisted of patients with different mutations. However, to the best of our knowledge, this is the first 10-year follow-up report of DE in LDS patients. As many of the participants in the cohort were related, the results should be interpreted with caution. Four patients had undergone fixation of the spine; this could be a confounding variable, but to omit these individuals would have led to selection bias. We did not consider the surgery to affect dura, and image artifacts due to fixation material did not hinder assessment of DE in the lumbosacral region. The hospital controls at baseline were neither suitable nor available for re-examination at the time of follow-up. A new control group therefore had to be found. The changes in the study group are hence not parallel to the differences between the two control groups, thus not comparable. Readings were performed by two radiologists in consensus; therefore, interobserver reliability was not tested. However, the method used has been validated previously [14], and two observers performing the readings in consensus should result in uniformity.

In the present study symptoms that might have been caused by DE were not correlated to our findings, this remains to be explored.

Clinical considerations

Our study and prior reports on DE support the view that MRI of the lumbosacral spine should be performed in patients with suspected MFS as a diagnosis of DE may have clinical consequences. Our findings show that DE can evolve during adulthood. This indicates that repeated imaging of the lumbosacral spine may be beneficial in patients with newly acquired symptoms thought to be related to DE, and in patients prior to spine surgery, spinal anesthesia and some pelvic interventions [17–29].

Conclusions

An increase in the number of MFS patients diagnosed with DE as well as with AM was observed after 10 years. All patients who developed AM had DE at baseline, hence MFS patients with known DE can develop a more severe form of DE in adulthood. LDS type 1, 2, and 3 may also have DE and develop AM in adulthood. According to the current diagnostic criteria for MFS, DE is one of seven systemic diagnostic features, but its diagnosis is hampered by lack of a uniform

choice of methods and cut-off values. We suggest using the criteria recommended by Lundby et al. [14], but with a threshold value for DSR S1 raised from 0.59 to 0.64 as a reasonable compromise between sensitivity and specificity. The results from the present study may help as guidance for appropriate follow-up of patients with dural ectasia.

Acknowledgments

This study has been funded by Roy Magnus Løkens Foundation for Medical Imaging; Department of Radiology and Nuclear Medicine, Oslo University Hospital; Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway; TRS, National Resource Centre for Rare Disorders, Sunnaas Rehabilitation Hospital, Nesoddtangen.

We want to thank Kai Andersen (Cardiology), Gunhild Falleth Sandvik and Liv Drolsum (Ophthalmology) who contributed with their investigations of organ manifestations related to the MFS diagnosis in this study. We also want to thank Odd Geiran (Cardiothorac Surgery), Kirsten Krogh-Sørensen (Vascular Surgery), Finn Lilleås (Radiology), Cecilie Røe and Johan Stanghelle (Physical medicine), for support and assistance which without, the study could not have been completed.

References

[1] Murphy-Ryan M, Psychogios A, Lindor NM. Hereditary disorders of connective tissue: a guide to the emerging differential diagnosis. Genet Med 2010;12:344–54.
[2] Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476–85.
[3] Avivi E, Arzi H, Paz L, Caspi I, Chechik A. Skeletal manifestations of Marfan syndrome. Isr Med Assoc J 2008;10:186–8.
[4] Groth KA, Hove H, Kyhl K, Folkestad L, Gaustadnes M, Vejlstrup N, et al. Prevalence, incidence, and age at diagnosis in Marfan Syndrome. Orphanet J Rare Dis 2015;10:153.
[5] von Kodolitsch Y, De Backer J, Schuler H, Bannas P, Behzadi C, Bernhardt AM, et al. Perspectives on the revised Ghent criteria for the diagnosis of Marfan syndrome. Appl Clin Genet 2015;8:137–55.
[6] Collod-Beroud G, Le Bourdelles S, Ades L, Ala-Kokko L, Booms P, Boxer M, et al. Update of the UMD-FBN1 mutation database and creation of an FBN1 polymorphism database. Hum Mutat 2003;22:199–208.
[7] Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. N Engl J Med 1979;300:772–7.
[8] Rand-Hendriksen S, Tjeldhorn L, Lundby R, Semb SO, Offstad J, Andersen K, et al. Search for correlations between FBN1 genotype and complete Ghent phenotype in 44 unrelated Norwegian patients with Marfan syndrome. Am J Med Genet A 2007;143a:1968–77.
[9] Vanem TT, Geiran OR, Krohg-Sorensen K, Roe C, Paus B, Rand-Hendriksen S. Survival, causes of death, and cardiovascular events in patients with Marfan syndrome. Mol Genet Genomic Med 2018;6:1114–23.
[10] Sheikhzadeh S, Sondermann C, Rybczynski M, Habermann CR, Brockstaedt L, Keyser B, et al. Comprehensive analysis of dural ectasia in 150 patients with a causative FBN1 mutation. Clin Genet 2014;86:238–45.
[11] Oosterhof T, Groenink M, Hulsmans FJ, Mulder BJ, van der Wall EE, Smit R, et al. Quantitative assessment of dural ectasia as a marker for Marfan syndrome. Radiology 2001;220:514–8.
[12] Habermann CR, Weiss F, Schoder V, Cramer MC, Kemper J, Wittkugel O, et al. MR evaluation of dural ectasia in Marfan syndrome: reassessment of the established criteria in children, adolescents, and young adults. Radiology 2005;234:535–41.
[13] Fattori R, Nienaber CA, Descovich B, Ambrosetto P, Reggiani LB, Pepe G, et al. Importance of dural ectasia in phenotypic assessment of Marfan's syndrome. Lancet 1999;354:910–3.
[14] Lundby R, Rand-Hendriksen S, Hald JK, Lilleås FG, Pripp AH, Skaar S, et al. Dural ectasia in Marfan syndrome: a case control study. AJNR Am J Neuroradiol 2009;30:1534–40.
[15] Ahn NU, Sponseller PD, Ahn UM, Nallamshetty L, Rose PS, Buchowski JM, et al. Dural ectasia in the Marfan syndrome: MR and CT findings and criteria. Genet Med 2000;2:173–9.
[16] Mesfin A, Ahn NU, Carrino JA, Sponseller PD. Ten-year clinical and imaging follow-up of dural ectasia in adults with Marfan syndrome. Spine J 2013;13:62–7.
[17] Foran JR, Pyeritz RE, Dietz HC, Sponseller PD. Characterization of the symptoms associated with dural ectasia in the Marfan patient. Am J Med Genet A 2005;134a:58–65.
[18] Nallamshetty L, Ahn NU, Ahn UM, Nallamshetty HS, Rose PS, Buchowski JM, et al. Dural ectasia and back pain: review of the literature and case report. J Spin Disord Tech 2002;15:326–9.
[19] Voermans NC, Hosman AJ, van Alfen N, Bartels RH, de Kleuver M, op den Akker JW, et al. Radicular dysfunction due to spinal deformities in Marfan syndrome at older age: three case reports. Eur J Med Genet 2010;53:35–9.
[20] Apetroae A, Strenzke T, Ferbert A, Schellinger PD. Spontaneous intracranial hypotension and Marfan syndrome. Nervenarzt 2016;87:846–52.
[21] Davenport RJ, Chataway SJ, Warlow CP. Spontaneous intracranial hypotension from a CSF leak in a patient with Marfan's syndrome. J Neurol Neurosurg Psychiatry 1995;59:516–9.
[22] Schievink WI. Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. JAMA 2006;295:2286–96.
[23] Schievink WI, Maya MM, Jean-Pierre S, Nuno M, Prasad RS, Moser FG. A classification system of spontaneous spinal CSF leaks. Neurology 2016;87:673–9.
[24] Jones KB, Erkula G, Sponseller PD, Dormans JP. Spine deformity correction in Marfan syndrome. Spine (Phila Pa 1976) 2002;27:2003–12.
[25] Lacassie HJ, Millar S, Leithe LG, Muir HA, Montaña R, Poblete A, et al. Dural ectasia: a likely cause of inadequate spinal anaesthesia in two parturients with Marfan's syndrome. Br J Anaesth 2005;94:500–4.
[26] Sakurai A, Miwa T, Miyamoto Y, Mizuno Y, Ka K. Inadequate spinal anesthesia in a patient with Marfan syndrome and dural ectasia. A A Case Rep 2014;2:17–9.
[27] Sahin N, Genc M, Kasap E, Solak A, Korkut B, Yilmaz E. Anterior sacral meningocele masquerading as an ovarian cyst: a rare clinical presentation associated with Marfan Syndrome. Clin Pract 2015;5:752.
[28] Schneider MB, Dittmar S, Boxer RA. Anterior sacral meningocele presenting as a pelvic/abdominal mass in a patient with Marfan syndrome. J Adolesc Health 1993;14:325–8.
[29] Guvendi B, Ogul H. Anterior sacral meningocele presenting as right adnexal cyst. Spine J 2016;16:e571.
[30] Rand-Hendriksen S, Lundby R, Tjeldhorn L, Andersen K, Offstad J, Semb SO. et al. Prevalence data on all Ghent features in a cross-sectional study of 87 adults with proven Marfan syndrome. Eur J Hum Genet 2009;17:1222–30.
[31] Shah LMM, Kevin R. Sacral mass, adult. In: Jhaveri MDS, Karen L, Ross Jeffrey S, Moore Kevin R, Osborn Anne G, Ho Chang Yueh, editors. ExpertDDX brain and spine. 2nd ed Elsevier; 2018. p. 222–5.
[32] De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62:417–26.
[33] Pierro A, Cilla S, Maselli G, Cucci E, Ciuffreda M, Sallustio G. Sagittal normal limits of lumbosacral spine in a large adult population: a quantitative magnetic resonance imaging analysis. J Clin Imaging Sci 2017;7:35.
[34] Currarino G, Coln D, Votteler T. Triad of anorectal, sacral, and presacral anomalies. AJR Am J Roentgenol 1981;137:395–8.

[35] Abello R, Rovira M, Sanz MP, Gili J, Capdevila A, Escalada J, et al. MRI and CT of ankylosing spondylitis with vertebral scalloping. Neuroradiology 1988;30:272–5.
[36] Eichhorn C, Wendt G, Staudte HW, Gilsbach JM. Dural ectasia in von Recklinghausen's disease of the lumbar spine: a case report. J Bone Joint Surg Br 1995;77:834–5.
[37] Salerno NR, Edeiken J. Vertebral scalloping in neurofibromatosis. Radiology 1970;97:509–10.
[38] Stern WE. Dural ectasia and the Marfan syndrome. J Neurosurg 1988;69:221–7.
[39] Chuzel Q, Dupuis-Girod S, Rousset M, Decharry C, Decullier E, Pialat JB. Assessment of dural ectasia using computed tomodensitometry as a criterion in Marfan syndrome. J Comput Assist Tomogr 2018;2:252–8.