

Hip Pain in Nonambulatory Children with Type-I or II Spinal Muscular Atrophy

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Background: The purpose of the present study was to define the prevalence of hip pain in nonambulatory children with spinal muscular atrophy (SMA) (type I or II) treated with aggressive medical management, prior to widespread use of disease-modifying therapies (DMTs).

Methods: A retrospective chart review (1993 to 2017) was performed on children diagnosed with SMA to identify subjective reports of hip pain and associated interventions, while radiographs were evaluated to assess hip instability and spinal deformity.

Results: Seventy-two patients (33 with type I and 39 with type II) met the inclusion criteria. Hip pain was more frequent in type-II SMA (49% versus 12%; p = 0.001). Seventeen percent of the patients with 2 copies of the SMN2 (survival motor neuron 2) gene, 53% of patients with 3 copies, and 1 of the 2 patients with 4 copies reported hip pain. Nearly all patients had abnormal findings on hip radiographs made at the onset of pain or at the latest follow-up; however, no patient with type-I and 18% of those with type-II SMA had pain that was severe enough to undergo invasive intervention (p = 0.01). The intervention reduced the pain in most of those patients but completely eliminated it in only 1 patient. No significant differences were found with respect to the mean age at the onset of scoliosis, the mean age at the time of scoliosis surgery, or whether insertion of growing rods or posterior spine fusion was performed between those with and without hip pain requiring invasive treatment.

Conclusions: This study is, to our knowledge, the largest investigation to date to assess hip pain among nonambulatory children with type-I or type-II SMA and suggests that symptoms rather than radiographs be utilized to direct care. These data will be crucial in assessing any effects that the new DMTs have on the natural history of hip pathology and pain in nonambulatory patients with SMA.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Solution of the SMN1 (survival motor neuron 1) gene, which leads to degeneration of the anterior horn cells of the site survival solutions with type-III SMA. SMA is caused by a mutation of the solution of the SMN1 (survival motor neuron 1) gene, which leads to generation of the anterior horn cells of the spinal cord^{4,5}.

modifying therapies (DMTs) that target these genetic pathways have been approved^{7,8} and have demonstrated dramatically improved motor function⁷⁻⁹ and event-free survival^{7,8}. The effects of these therapies on the orthopaedic manifestations of the disease are not yet known.

Prior to the introduction of DMTs for SMA, comprehensive multidisciplinary medical approaches were utilized at some centers to increase the life expectancy for children with SMA¹⁰⁻¹². With extended life expectancy, children with type-I or type-II SMA often develop scoliosis and hip subluxation or dislocation^{13,14}. While the benefits of instrumented spinal fusion and/or growing rods to stabilize the spinal deformities have been demonstrated¹⁵⁻¹⁹, the best treatment for hip pathology in these nonambulatory children has been controversial, ranging from observation²⁰ to aggressive surgical management^{21,22}. Over

Disclosure: The Disclosure of Potential Conflicts of Interest forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A411).

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the past 2 decades, we have performed aggressive medical management and management of spinal deformities in these children, while only symptomatically treating the hip pathology. The goal of this study was to define the overall prevalence and risk factors of hip pain in our nonambulatory patients with type-I or II SMA, prior to the widespread use of DMTs.

Materials and Methods

Sample

A retrospective chart review was performed at a single institution to assess hip pain in children with SMA treated from 1993 to 2017. Institutional review board approval was obtained prior to the study. Patients were identified through the electronic medical records with International Classification of Diseases, Ninth Revision (ICD-9) codes for SMA (335, 335.1, 335.10, 335.11, and 335.19). Only nonambulatory patients with >2 years of clinical follow-up were included. Exclusion criteria included a diagnosis of type-III SMA, an incomplete medical record, or no orthopaedic evaluation. Patients in this cohort were studied prior to the availability of DMTs.

Medical Record Review

Medical records were reviewed for anthropometric measures, SMA type, SMN2 copy number, and diagnostic method. Similarly, the presence of scoliosis, history of spinal instrumentation, type of instrumentation, and level of instrumentation were recorded. Notes were used to identify subjective reports of hip pain by retrospective review. Pain scores (on a Likert-type scale from 0 to 10) and/or pain medications were recorded from the visit in which the patient reported hip pain and/or at the last follow-up. Severe hip pain was defined as hip pain requiring a steroid injection or operative treatment. Procedural and operative reports were reviewed to identify invasive treatments performed to alleviate hip pain or correct spinal deformity. If exact dates of spinal surgery were not available, December 31 of the year of surgery was used to allow calculations. Available pelvic and spinal radiographs were evaluated for the status of the hips at the last follow-up and, in patients with hip pain, the status of the hip at the time that the pain was reported. Hip subluxation was defined as any lateral migration of the femoral head out from under the acetabulum or a break in the Shenton line as determined by a fellowshiptrained pediatric orthopaedic surgeon (M.A.H.). Individual hips were scored as reduced (0), subluxated (1), or dislocated (3), and the hip status was reported as the sum of both hips to provide a score ranging from 0 to 6 (without 5) (Fig. 1-A). Cobb angles and pelvic obliquity preoperatively and at the last follow-up were measured by the same fellowship-trained pediatric orthopaedic surgeon. These variables were then used to determine the overall prevalence of hip pain and associated risk factors in our patients.

Statistical Analysis

Demographic and clinical variables, including sex, SMA type, spinal instrumentation, hip status, and hip pain, were compared. The Fisher exact test was used to compare categorical variables, and the Student t test was used as indicated for continuous variables. Odds ratios (ORs) with Haldane-Anscombe correction when necessary were calculated to assess the risk of developing hip pain, given these variables.

Source of Funding

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Results

Demographics

A mong 120 patients with SMA receiving care at our institution over the study period, 72 patients (33 with type I and 39 with type II) met the inclusion criteria. Forty-four female and 28 male patients were included in the cohort. The SMA diagnosis was confirmed in 96% of the patients with genetic (n = 61) or electromyographic and/or muscle biopsy evidence (n = 8). The mean length of follow-up within our system was 10.4 years (range, 3.7 to 22.8 years), with a mean (and standard deviation) of 8.3 ± 3.3 years for the type-I group and 12.2 ± 5.1 years for the type-II group. The mean age at the time of the first and last clinic visits was 1.2 ± 1.8 and 9.6 ± 3.9 years, respectively, for the type-I group and 3.6 ± 4.2 and 15.8 ± 6.6 years for the type-II group.

Hip Pain

Twenty-three (32%) of the 72 patients reported hip pain at some point in their clinical course. Hip pain was more common in the 39 patients with type-II SMA (19 [49%]) than in the 33 who had type-I SMA (4 [12%]; p = 0.001). The mean age at the onset of any hip pain was 8.0 ± 3.9 years in the type-I SMA group and 9.0 ± 4.4 years in the type-II SMA group (p = 0.56). Forty-five of the 72 patients had an SMN2 copy number available for analysis. Seventeen percent (4) of the 24 patients with 2 SMN2 copies, 53% (10) of the 19 patients with 3 SMN2 copies, and 50% (1) of the 2 patients with 4 SMN2 copies reported hip pain.

Radiographic Hip Status

Thirty-one of 33 patients with type-I and 35 of 39 with type-II SMA had radiographs (pelvic, scoliosis, and/or abdominal radiographs) that allowed the review of 136 hips. All patients with type-I SMA and 97% (all but 1) of the patients with type-II SMA had abnormal findings on hip radiographs (a hip status of >0) at the onset of pain or at the last follow-up. Hip status did not differ significantly among patients with no pain compared with any pain for type-I SMA (p = 0.42) and for type-II SMA (p = 0.75) (Fig.1-B, Table I). In addition, no difference in radiographic hip status was detected in patients with type-II SMA with no or mild pain compared with those with severe pain (p = 0.55) (Fig.1-B, Table I). Of the 7 children with severe pain, 5 had pain bilaterally and 2 had pain on the right side. Two of these patients had bilateral hip dislocations, 3 had bilateral hip subluxations, and 2 had 1 hip with subluxation and 1 normally reduced hip. The 2 patients with unilateral pain had bilateral dislocations.

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Fig.1

Figs. 1-A and 1-B Radiographs showing examples used for scoring and a chart showing the hip status of the 72 patients. **Fig. 1-A** Examples of each hip status score (0, 1, 2, 3, 4, and 6) defined as the sum of the bilateral hip scores, in which each hip is scored as reduced (0), subluxated (1), or dislocated (3). **Fig. 1-B** Hip status by SMA type and hip pain. Two patients with type-I SMA (SMA 1) and no pain, 3 patients with type-II SMA (SMA 2) and no pain, 1 patient with type-II SMA and any pain, and 1 patient with type-II SMA and severe pain did not have hip status score available.

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TABLE I Comparison of Variables Among the Groups with Nonsevere Pain or Severe Pain and the Group with No Pain*										>
	Age at Time of Last Follow-up† (<i>yr</i>)		Age at Onset of Hip Pain† <i>(yr)</i>		Age at Onset of Severe Hip Pain (i.e., at Time of 1st Procedure)† (yr)		Hip Status†		Age At Time of Hip Radiographic Assessment† (yr)	
	SMA I	SMA II	SMA I	SMA II	SMA I	SMA II	SMA I	SMA II	SMA I	SMA II
No pain	9.1 ± 3.2	$16.2\pm7.7\S$	NA	NA	NA	NA	6 (1-6)	2,4,6 (0-6)#	7.4 ± 3.1	11.4 ± 5.9 §
Nonsevere pain	12.1 ± 5.3	16.4 ± 6.0	$\textbf{8.0}\pm\textbf{3.9}$	10.1 ± 5.0	NA	NA	2 (2-6)	1 (1-6)	7.9 ± 4.0	12.2 ± 4.4
Severe pain	NA	13.7 ± 2.8	NA	7.2 ± 2.4	NA	9.2 ± 1.8	NA	2 (1-6)	NA	7.9 ± 2.0††

*The group with type-I spinal muscular atrophy (SMA I) had 33 patients (16 who had spine surgery), and the group with type-II SMA (SMA II) had 39 patients (30 who had spine surgery). NA = not applicable. \dagger The values are given as the mean and the standard deviation. For patients who underwent spine surgery, preoperative and postoperative values were used for pelvic obliquity and Cobb angle, whereas for patients who did not undergo spine surgery, the last follow-up measurements were utilized for pelvic obliquity and Cobb angle. \dagger The values are given as the mode, with the range in parentheses. Individual hip scoring was defined as 0 if the hip was reduced; 1, subluxated; and 3, dislocated, and the sum of both hips indicated the hip status. \$P < 0.05 in comparing SMA-I and SMA-II groups with no pain. #This was a trimodal distribution with equal numbers having 2, 4, 6 as hip scores. **P < 0.05 between SMA-II and SMA-I patients with nonsevere pain. $\dagger \dagger P < 0.05$ between SMA-II patients with nonsevere pain.

Scoliosis and Spinal Instrumentation

All 72 patients included in the study had spinal radiographs. At the latest follow-up, 69 patients (one of whom had fusion on all available radiographs and was assumed to have scoliosis) were diagnosed with scoliosis, and 46 of the 72 patients had spinal instrumentation. Seventeen (37%; 2 of 16 with type-I and 15 of 30 with type-II SMA) of the 46 patients with instrumentation had hip pain, while 6 (23%; 2 of 17 with type-I and 4 of 9 with type-II SMA) of the 26 patients without instrumentation had hip pain (p = 0.2959). There was no significant difference between those with and without any hip pain with respect to age at the onset of scoliosis (mean, 7.02 ± 3.0 versus 6.3 ± 2.1 years; p = 0.39) or at the time of surgery (8.0 ± 2.3 versus 7.27 ± 3.9 (p = 0.8).

Of the 46 patients who had spinal instrumentation, 23 had spinal fusions and 23 had growing-rod insertions. After accounting for SMA type, there was no significant difference with respect to the age at the onset of scoliosis or hip pain, maximum preoperative or postoperative Cobb angle, or pelvic obliquity (Table I).

Of the 16 patients with type-I SMA who had instrumentation, 2 (both with growing rods) had hip pain. Of the 30 patients with type-II SMA who had instrumentation, 15 patients (9 who had spinal fusions and 6 who had growing rods) had hip pain. Of the total of 46 patients with instrumentation, 17 (8 with type-I and 9 with type-II SMA) had instrumentation above the pelvis, and the remaining 29 patients had instrumentation to the pelvis. Only 3 (18%) of the 17 patients with instrumentation and pain had instrumentation above the pelvis, whereas the remaining 14 (82%) had instrumentation to the pelvis (OR, 3.5; p = 0.02) (Table II). Five of the 7 patients with severe pain had instrumentation to the pelvis, and the remaining 2 patients with severe pain had no spinal instrumentation. The duration of follow-up was a mean of 8.6 ± 4.1 years for patients with instrumentation to the pelvis compared with a mean of 6.9 ± 5.8 years for patients with instrumentation above the pelvis (p = 0.25).

Hip Pain and Treatment

Twenty-three of 72 patients reported pain (Fig. 2). The mode of the clinical pain scores (adjusted to a scale from 0 to 10) for the 16 patients who did not undergo invasive treatment was 0 (range, 0 to 2) at the time that pain was reported and 0 (range, 0 to 1) at the last follow-up (Fig. 2-B). Most of these patients were managed with over-the-counter medications, positioning and changes in durable medical equipment, or observation (Fig. 2-D). No patient with type-I SMA but 7 (18%) of those with type-II SMA had symptoms severe enough to undergo an invasive procedure for relief (p = 0.01). The mode of their pain scores was 2 (range, 0 to 10) at the time of their procedure (Fig. 2-C). Five of these 7 patients had been prescribed narcotic medications in an attempt to treat their pain prior to the invasive treatment (Fig. 2-D). At the time of final follow-up, pain scores had improved in all 7 patients following intervention, with a mode of 0 (range, 0 to 1) (Fig. 2-C); however, 4 of these patients remained on narcotics following invasive intervention.

Invasive treatment for pain included intra-articular injections (n = 6), spinal implant revision (n = 2), and proximal femoral resection (n = 1; Fig. 3). Treatment reduced pain in most patients; however, it was completely, but subjectively, eliminated in only 1 patient despite most rating their pain a zero elsewhere within the clinical record. Of the surgical patients, 1 underwent a bilateral sacroiliac spinal fusion rod removal. A second patient initially had intra-articular injections, which temporarily reduced the pain; however, this patient had multiple recurrences of hip pain with multiple subsequent procedures, including the removal of sacroiliac implants, bilateral adductor tenotomies and right-sided open psoas release, and bilateral proximal femoral valgus osteotomies and femoral head

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	TABLE I (continued)								
Age at Time of Scoliosis Surgery† (yr)		Pelvic Obliquity (Preop. or Last Follow-up)† (deg)		Postop. Pelvic Obliquity† (deg)		Cobb Angle (Preop. or Last Follow-up)† (deg)		Postop. Cobb Angle† (deg)		
	SMA I	SMA II	SMA I	SMA II	SMA I	SMA II	SMA I	SMA II	SMA I	SMA II
	6.5 ± 2.5	8.6 ± 4.7	14.7 ± 14.1	20.4 ± 23.3	8.5 ± 3.6	10.3 ± 15.9	47.2 ± 3.6	55.0 ± 35.1	24.8 ± 3.6	38.4 ± 29.6
	5.7 ± 2.3	$\textbf{8.6} \pm \textbf{2.0}$	9.3 ± 13.1	20.5 ± 10.3	26.3 ± 27.8	$8.3\pm7.5^{**}$	34.7 ± 26.9	46.7 ± 19.7	30.4 ± 16.5	24.6 ± 18.5
	NA	8.0 ± 2.5	NA	22.4 ± 5.0	NA	10.9 ± 6.8	NA	58.1 ± 12.4	NA	31.5 ± 24.5

resections. After the femoral head resections, the pain was initially reduced but then returned. Sacroiliac instrumentation was prominent in these patients and was removed to eliminate implant prominence as a source of pain. The mean length of follow-up following the last intervention for these 7 patients was 4.52 ± 2.1 years.

Discussion

R adiographic hip pathology was found in nearly every nonambulatory patient with SMA in our study. Thirty-two percent (23) of 72 patients reported hip pain at some point during their clinical course. This pain occurred >4 times as often in children with type-II SMA (19 [49%] of 39) than in those with type-I SMA (4 [12%] of 33). Our institution's aggressive multidisciplinary treatment of these medically frail children over the past 2 decades, prior to the widespread use of DMTs, allowed this to be the largest, most homogeneous, nonambulatory SMA cohort to be assessed for hip pain. Previous studies have increased sample sizes by combining patients who had SMA with those with other neuromuscular disorders²²⁻²⁴ or have mixed both ambulatory and nonambulatory patients with SMA^{25,26}, which may have confounded their results. Sporer and Smith, who combined ambulatory patients with type-III and nonambulatory patients with type-II SMA (n = 41), reported that 45% of the subjects had radiographic hip pathology and only 2 (5%) reported hip pain at a mean follow-up of 14 years²⁶. In addition, Xu et al., who also combined ambulatory and nonambulatory patients (n = 104), found that 58% of patients reported hip pain²⁵. Given the more functionally uniform (nonambulatory), but medically frail, patients in our study, our mean follow-up of 10.4 years and sample size compare favorably with these studies and are larger and longer than those in other published studies describing hip pain in patients with SMA^{14,20,23,26}. Ours is the only study to date, as far as we know, to describe specifically patients with type-I and type-II SMA.

Prior to the introduction of DMTs, controversy surrounded the treatment of hip subluxation and dislocation in SMA because of complications associated with surgery and the risk of recurrent hip dislocation after surgical intervention²⁶. Shapiro and Bresnan recommended proximal femoral varus derotational osteotomies for nonambulatory children

	Any Pain		Severe Pain		
	Odds Ratio (95% CI)	P Value†	Odds Ratio (95% CI)	P Value†	
Type-I SMA	0.15 (0.04, 0.49)	0.0019	NAŧ		
Type-II SMA	6.90 (2.0, 23.3)	0.0019	NAŧ		
2 copies of SMN2 gene	0.18 (0.05, 0.72)	0.015	0.26 (0.02, 2.7)	0.26	
3 copies of SMN2 gene	4.40 (1.23, 15.81)	0.023	4.88 (0.47, 50.98)	0.19	
Scoliosis surgery	1.95 (0.66, 5.82)	0.23	1.46 (0.26, 8.14)	0.66	
Growing rods	1.21 (0.42, 3.46)	0.72	1.69 (0.35, 8.25)	0.52	
Spinal fusion	1.61 (0.57, 4.56)	0.37	0.84 (0.15, 4.68)	0.84	
Instrumentation above pelvis	0.38 (0.10,1.46)	0.16	0.18 (0.01, 3.41)	0.19	
Instrumentation to pelvis	3.53 (1.25, 9.92)	0.017	4.27 (0.77, 23.74)	0.10	
No spinal instrumentation	0.51 (0.17, 1.52)	0.23	0.683 (0.12, 3.80)	0.66	

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Fig. 2

Figs. 2-A through 2-D Histograms of the reported hip pain and the noninvasive management of the pain. F/U = follow-up. **Fig. 2-A** The overall number of patients with no pain at any time, nonsevere pain, and severe pain. **Fig. 2-B** Pain scores at the onset of hip pain and at the last follow-up visit for the cohort who had nonsevere pain. **Fig. 2-C** Pain scores at the day of intervention and at the last follow-up in the cohort with severe pain. (All scores are reported on a scale of 0 to 10; the results for the 1 patient who had been given a 5-point scale were normalized to a 10-point scale for comparison.) **Fig. 2-D** Noninvasive management of hip pain recommended at the onset of hip pain in the cohort with severe pain and that with nonsevere pain. One asterisk indicates bed, padding, or chair modification needed, and 2 asterisks indicates that "pain medications" were reported for 1 patient with no prescription and assumed to be acetaminophen or an NSAID (nonsteroidal anti-inflammatory drug). NA = pain scores not available, and DME = durable medical equipment.

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Outcomes of patients with type-II SMA who had severe pain. The arrow indicates 1 patient in the steroid injection group who received a steroid injection with only temporary relief and underwent spinal implant revision and multiple other procedures. One other patient underwent spinal implant revision but never received a steroid injection.

with SMA and hip subluxation²¹, and more recently, others have advocated for similar surgery to correct pelvic obliquity and prevent scoliosis progression²⁴. However, Zenios et al. noted that the majority of patients with type-II or type-III SMA and hip subluxation did not have pain²⁰. Furthermore, that group found that only 1 of 9 patients who underwent hip surgery reported any quality-of-life improvement and recommended against surgical intervention. While we found a high prevalence of radiographic hip pathology in our patients, fewer than half reported hip pain and even fewer could not be medically managed with a steroid injection (Fig. 3). Therefore, we concluded that not every abnormal finding in a hip radiograph of a patient with SMA requires surgery. However, if risk factors such as type-II SMA scoliosis requiring instrumentation to the pelvis, or recurrent pain following steroid injections, are present, surgical intervention may be considered.

The association between the spine and hip pain in patients with neuromuscular conditions may be conceptualized by the "triadic complex," which describes the relationship among scoliosis, pelvic obliquity, and hip subluxation-dislocation⁹. In our patients, we found that scoliosis developed at the same time as or before hip pathology and that scoliosis was always present prior to the onset of hip pain. While we did not find any associations among curve magnitude, pelvic obliquity, or instrumentation type with hip pain, instrumentation to the pelvis was found to be a significant risk factor (OR, 3.53; p = 0.017).

Although this study is the largest to date in this rare population, it was limited by patient volume and its retrospective nature in assessing hip pain. Validated pain scores and other objective measures were not used to rate pain; instead, we relied on the patient or family, particularly those of nonverbal patients, from whom we collected reports of pain over many years. The exact source of the pain in patients with spinal instrumentation to the pelvis (hip versus the sacroiliac joint) was also difficult to discern. In addition, evaluating interventions for pain at outside centers was not possible. These factors underestimate the prevalence of pain in this population. Furthermore, it was difficult to discern the intensity and duration of the pain from the chart review, and correlation between pain intensity and type of pain medication prescribed was not determined. Without having validated pain or quality-of-life scores for each child dating back 2 decades, we included any reported hip pain and used a more objective proxy available within the chart, the willingness to undergo an invasive treatment, to define "severe pain." While this may be an imperfect

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measure, we thought this to be a reasonable proxy for pain severe enough to affect quality of life, as any invasive procedure requiring anesthesia in this fragile population carries risk. However, we acknowledge that patients who did not undergo a procedure can also have severe pain. Other confounding factors that contribute to pain, including contractures and tone, require further study.

With the recent U.S. Food and Drug Administration approval of DMTs, understanding the effects that these therapies will have on SMA-related orthopaedic pathology is challenging. These therapies may make an already small population more heterogeneous, depending on which therapies, at which age and disease state and in which combination, each patient receives. As these DMTs are potentially life-saving, withholding such treatments to prospectively evaluate their effects on orthopaedic outcomes is unethical. Thus, despite the limitations of the current study, the data presented will be extremely useful as a control, in monitoring the effects that these treatments have on the prevalence of spine and hip pathology. Our findings that the prevalence of hip pain was increased with an increased SMN2 copy number suggests that patients on DMTs that amplify the SMN2 gene pathway will likely become more symptomatic as they gain increased muscle tone with treatment.

In summary, this is the largest study to document the prevalence of hip pain in severely affected, nonambulatory children with type-I or type-II SMA. Nearly all patients developed radiographic hip pathology, and 32% reported hip pain at a mean age of 8.86 years, with <10% having enough pain to seek an

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invasive intervention. Patients with type-II SMA, with increased SMN2 copy number, and with spinal instrumentation to the pelvis appear most likely to report hip pain. This study offers baseline data for hip pathology and pain as the medical treatment of SMA transitions to DMTs.

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