Orthopaedic Management of Leg-length Discrepancy in Proteus Syndrome: A Case Series

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Introduction: Proteus syndrome (PS) is a rare mosaic disorder comprising asymmetric bony and soft tissue overgrowth leading to significant morbidity. Placement of growth inhibition hardware with subsequent epiphyseal arrest improves leg-length and angular deformities in pediatric patients without PS. The purpose of this study was to review the surgical approach and present outcomes, complications, and recommendations in 8 patients with PS and leg-length discrepancy (LLD).

Methods: We conducted a retrospective chart review of 8 patients with PS whose primary reason for surgery was LLD. Patients were eligible if they met clinical diagnostic criteria for PS and if the National Institutes of Health team performed at least 1 of their surgical interventions between 2005 and 2015. Surgical techniques included growth inhibition, with tension band plates, applied ≥ 1 times, and epiphyseal arrest.

Results: Eight patients, followed for an average of 4.6 years (range, 1.0 to 7.1 y) after the index procedure, were included in this analysis. Average age at first LLD surgery was 9.4 years (range, 6.1 to 13.6 y); the average LLD was 3.4 cm (range, 0.4 to 7.0 cm) at presentation, and 5.0 cm (range, 1.8 to 10.0 cm) at the time of the first LLD surgery. Participants underwent 23 total surgeries (range, 1 to 5 per patient) and 7 patients have completed surgical intervention. For the 7 patients who did not require overcorrection the average LLD at the last clinical encounter was 2.6 cm (range, 0.6 to 7.2 cm). We encountered 2 complications: 2 patients developed mild knee valgus, which responded to standard guided growth techniques.

Conclusions: This case series suggests that growth inhibition and epiphyseal arrest in children with PS can reduce LLD with few complications. Careful monitoring, rapid mobilization, deep venous thrombosis prophylaxis, and sequential compression devices were also integral elements of our surgical protocol.

Level of Evidence: Level IV.

Key Words: Proteus syndrome, leg-length inequality, epiphyseal arrest, growth inhibition, child

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BACKGROUND

Proteus syndrome (PS) is a rare mosaic genetic disorder characterized by progressive and sporadic overgrowth. Although children with PS typically appear normal at birth, disproportionate growth of bone and soft tissue is usually identified by 6 to 18 months of age.[1,2] PS is caused by a somatic activating mutation in the oncogene *AKT1*; diagnosis is confirmed by using the criteria in Table 1.[3]

The overgrowth in patients with PS is asymmetric, distorting, and relentless with a rate and severity that vary greatly among patients.[2,4] Overgrowth can affect any tissue or organ system, but particularly affects the skeleton.[1,4] Common lower extremity manifestations include leg-length discrepancy (LLD), varus and valgus angular deformities, internal and external tibial torsion, severe patellar overgrowth, joint contractures, and iliotibial band contractures.[4] Figure 1 illustrates several of the

TABLE 1. Proteus Syndrome Diagnostic Criteria

General criteria
Mosaic distribution
Progressive course
Sporadic occurrence
Specific criteria
Category A
Cerebriform connective tissue nevus
Category B
Linear epidermal nevus
Asymmetric, disproportionate overgrowth of 2 of the following
Limbs, skull, external auditory canal, vertebrae, or viscera
Specific tumors in the first decade of life
Bilateral ovarian cystadenomas
Monomorphic parotid adenomas
Category C
Dysregulated adipose tissue
Vascular malformations of ≥ 1
Capillary, venous, and/or lymphatic
Lung bullae
Facial phenotype
Long face, dolichocephaly, downslanted palpebral fissures, low nasal bridge
Wide or anteverted nares
Open mouth at rest

Diagnosis requires all 3 general criteria plus 1 criterion from category A, 2 from category B, or 3 from category C.[1]

lower extremity manifestations seen in this disorder. In addition, PS patients are at high risk for severe scoliosis and loss of joint mobility.

Orthopaedic interventions are often indicated in children with PS. Despite the debilitating nature of this disorder, there is little literature to direct orthopaedic management. Among children without underlying overgrowth syndrome, prior research has confirmed the efficacy of growth inhibition techniques for angular deformities and LLDs.[5,6] Tosi et al[4] discussed the promising potential of growth inhibition to manage patients with PS, but, no publications have empirically demonstrated its effectiveness.

The purpose of this paper is to present a case series of 8 patients with PS who were managed via growth inhibition and/or epiphyseal arrest at the National Institutes of Health (NIH) and the Shriners Hospital for Children-Houston for LLD. We will discuss our surgical protocols, outcomes, complications, and recommendations.

METHODS

We reviewed the cohort of pediatric PS patients (N = 48) followed at the National Human Genome Research Institute of NIH and identified 8 patients with PS who had been treated for LLD using growth inhibition and/or epiphyseal arrest and underwent surgery at the NIH Clinical Center between 2005 and 2015. Patients were eligible for inclusion if they met the clinical diagnostic criteria for PS (Table 1) and if the NIH team performed at least one of their surgical interventions. Erect, anterior posterior radiographs of the lower extremities supplemented with scanograms were used to assess LLD and to assist surgical planning. X-rays of the

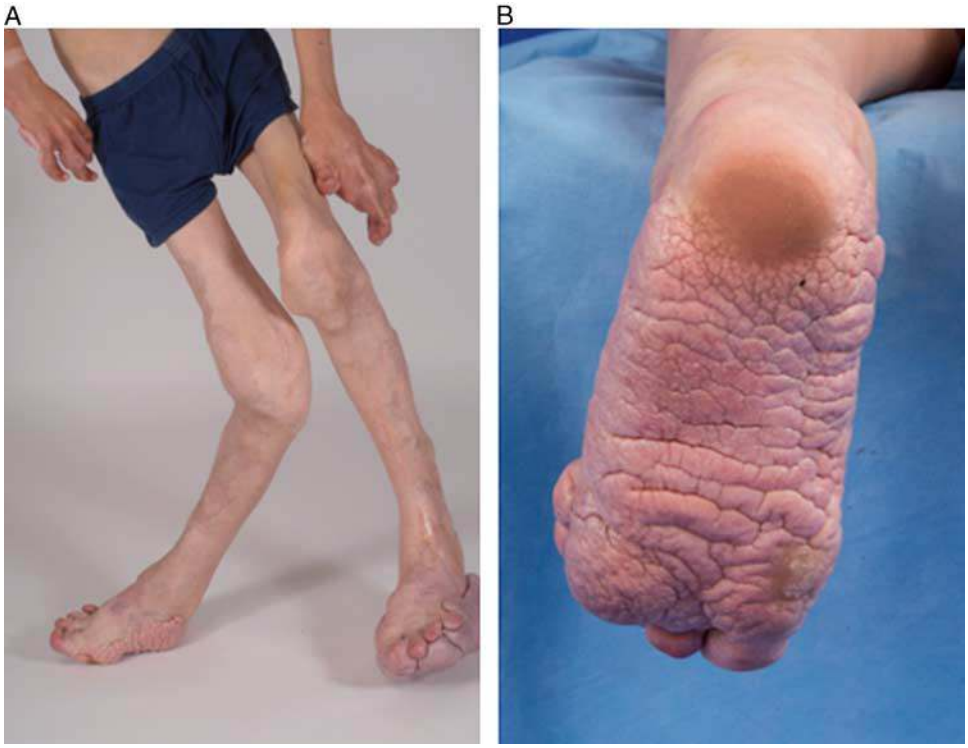

FIGURE 1. Lower extremity manifestations other than leg-length discrepancy in patients with Proteus syndrome: angular distortion (A) and the cerebriform connective tissue nevus (B). Patient PS64.3 at age 16.7 years (B). full color online

hands and wrists were used to estimate skeletal age using the Greulich and Pyle Atlas.[7]

Surgical techniques included growth inhibition, using tension band plating, and epiphyseal arrest.[8,9] A single tension band plate was used for all patients except one. All patients were enrolled in the 94-HG-0132 IRB-approved protocol of the National Human Genome Research Institute.

RESULTS

Four males and 4 females were included in this analysis. The average age at the first surgery to address LLD was 9.4 years (range, 6.1 to 13.6 y), and the average LLD was 3.4 cm (range, 0.4 to 7.0 cm) at presentation, and 5.0 cm (range, 1.8 to 10.0 cm) at the time of the first LLD surgery. Participants were followed for an average of 4.6 years (range, 1.0 to 7.1 y) following the index procedure and underwent 23 total surgeries (range, 1 to 5 per patient). Brief clinical descriptions of each patient's initial presentation, LLD, and subsequent interventions are provided in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/BPO/A141). In addition, Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/BPO/A142) provides a summary of each patient's surgical interventions and LLD over time. Patients are presented in the order of enrollment.

The unpredictable natural history of LLD in this disorder is illustrated in Figure 2. Although 3 of the 8 patients developed a relatively mild LLD of ≤ 3.0 cm or less (PS52.3, PS83.3, and PS122.3), the other 5 patients developed a discrepancy of above 3.0 and up to 12.0 cm. See Figure 3 for a demonstration of the rapid progression of the LLD observed in patient PS73.3. In all 8 patients, interventions resulted in a decreased LLD from the maximum observed. For the 7 patients who did not require overcorrection, the average LLD at the last clinical encounter was 2.6 cm (range, 0.6 to 7.2 cm); however, only 2 of the total 8 patients had reached skeletal maturity. See Figure 4 for radiographs of patient PS78.3 at presentation and just before final surgery. One patient, PS87.3, was still undergoing active monitoring and treatment for his LLD at this writing, and no further interventions for LLD were planned in the other 7 patients; however, they were undergoing continued monitoring as they completed growth. One patient (PS101.3) underwent most of her surgeries at Shriners Hospital for Children-Houston. She required overcorrection to compensate for overgrowth of the foot on the affected side (Fig. 5).

Two patients developed knee valgus (PS87.3 and PS101.3) which responded to guided growth techniques, namely removal of the tension band laterally until the valgus had corrected; and 1 patient's (PS101.3) LLD needed to be overcorrected to compensate for overgrowth of the foot.

DISCUSSION

The clinical reports provided in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/BPO/A141) underscore the heterogeneity of manifestations of PS and the level of individualized treatment required in this disorder. Currently, there are no clear ways to identify children with PS at risk for developing extreme LLD at an early age. However, our case series suggests that a marked delay in bone age compared with chronological age may be indicative of more severe LLD over time. Unfortunately, traditional strategies for predicting final LLD such as growth remaining are not useful as children with

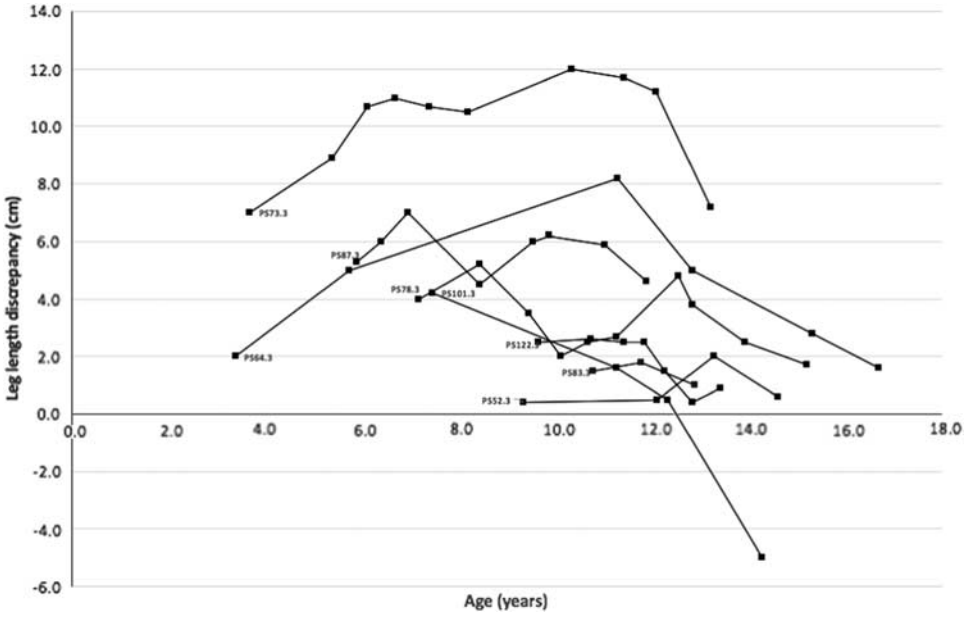

FIGURE 2. Leg-length discrepancy progression at increasing ages for 8 patients with Proteus syndrome.

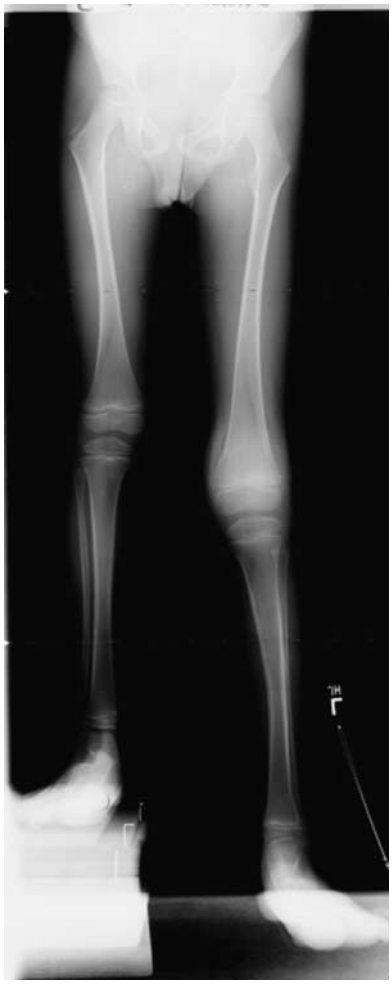

FIGURE 3. Patient PS73.3 at age 5.4 years. Although this patient had no evidence of a LLD at birth, by 5.4 years, his LLD was 8.9 cm. This image demonstrates the severe and rapid progression of LLD sometimes noted in patients with Proteus syndrome. LLD indicates leg-length discrepancy.

PS experience extraordinary growth spurts, when LLD worsening can be abrupt and extreme.

Medical complications of PS can seriously threaten recovery and are therefore relevant to orthopaedic management. Patients with PS are at high risk for developing deep venous thrombosis (DVT) and pulmonary embolism (PE), bullous lung disease, and restrictive lung disease, all of which increase the risk of complications in the perioperative period.[4,10,11] Turner et al[2] estimated that 30% of patients who met clinical diagnostic criteria for PS died prematurely from PE, postoperative complications, and pneumonia. In a recent review of 57 patients with PS, 6 of 10 deaths (60%) were the result of a DVT and bilateral PE at a young age (median age of 17 y), and among living patients, 6 of 47 (16%) had DVTs, with 3 of 6 having co-occurrence of PE. Among some deceased patients and in all those living, the recognized DVT/PE events occurred postoperatively in an affected (overgrown) limb.[12]

To mitigate these risks, all patients treated at the NIH were managed with DVT prophylaxis of 0.5 mg/kg enoxaparin (Sanofi Aventis US, Bridgewater, NJ) q12h IM, sequential compression devices until the patient was reasonably ambulatory, and all were mobilized quickly postoperatively. Although no patients in this series developed a perioperative DVT or PE, this is a common problem in patients with PS and the absence of this complication in this case series is noteworthy. We hypothesize that this trend is attributable to consistent prophylaxis and aggressive postoperative ambulation. Physical therapy has been shown to be essential to return to function after insertion of tension band plates in patients without PS.[13] All patients in this series also received physical therapy within a few days of surgery.

Others have described challenges in managing patients with PS and the potential for poor surgical outcomes and severe complications.[14] As underscored by our vignettes, periodic monitoring of the LLD is key because of the potential for rapid, spontaneous overgrowth that requires urgent surgical correction. Poor surgical outcomes in patients with PS have been reported in the literature. For example, Raboudi et al[14] performed a valgus proximal tibial osteotomy in a 6-year-old girl with PS and postsurgically, the patient developed extensive, severe soft tissue loss and exposed bone.

We encountered 2 complications: patients PS87.3 and PS101.3 developed mild knee valgus, which was managed by standard guided growth techniques. Technically, based on scanogram data, 1 patient (PS101.3) was overcorrected. However, this patient required extracorrection because of the extreme overgrowth of her foot on the involved side. This outcome underscores another aspect of treating patients with PS: although most often surgeons can limit their measurements to the long bones, in these patients, it is essential to include the pelvis and feet in the LLD analysis.

Timing for intervention evolved over the course of this study. As we recognized that we could not easily predict who would develop severe LLD, we moved toward earlier use of growth inhibition once the children had developed a LLD of over 1.5 cm if they were presumed to be at least 3 to 4 years away from the onset of puberty. Bone age x-rays were largely of limited use in operative planning because several children had extreme growth spurts as they neared skeletal maturity. We found that extreme height and early pubertal changes could suggest that a child was closer to the end of growth than they actually were. The natural history of PS is the relentless progression of overgrowth in affected body parts. As such, it is also important to recognize that tension band plating did not substantially improve the patients' LLD, but rather stabilized the overgrowth of the affected leg until the children were old enough to undergo epiphyseal arrest. This finding is consistent with other reports, which underscore that tension band plating is not as successful as epiphyseal arrest for correcting LLD. In contrast, in our series, tension band plating was effective for inhibiting further increases in extreme LLD until such time as epiphyseal arrest was appropriate.[15,16]

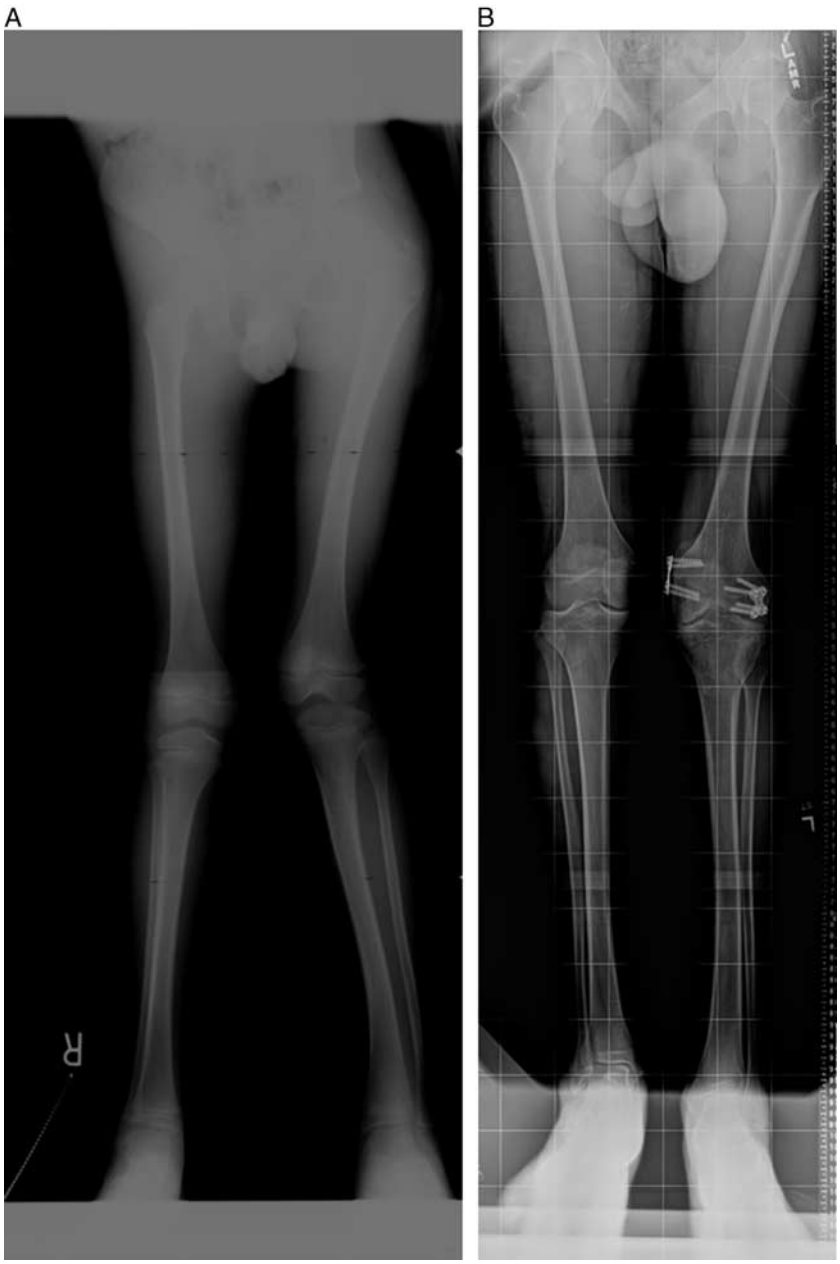

FIGURE 4. A, Patient PS78.3 at presentation (age, 7.2 y). B, Same patient just before his final surgery to remove the 8-plates from the medial and lateral, left distal femur (age, 15.2 y).

It is important to be aware of several other factors when evaluating or operating on an individual who may have PS. First, PS diagnosis should be established via specific criteria (Table 1), as our recommendations are applicable only to individuals with confirmed cases of this disorder. Turner et al[2] have demonstrated that children with segmental overgrowth are frequently misdiagnosed. Moreover, standard genetic testing using blood samples will fail to diagnose PS as the *AKT1* mutation is typically only present in clinically affected tissues.[2,3] All children in this case series met the strict criteria for PS diagnosis.

Finally, it is important to reiterate that PS is an overgrowth disorder. In all cases the shorter limb was more normal than the longer one. Interventions should focus on limiting the overgrowth of the longer leg.[4] Lengthening the shorter leg has the potential to render the shorter (more normal) leg more fragile, creating limbs that are far too long for the patient's trunk height, especially in a child that is excessively tall.

One of the major challenges was accurate measurement of the LLD. Our radiographic technique evolved over the course of this case series. We initially performed

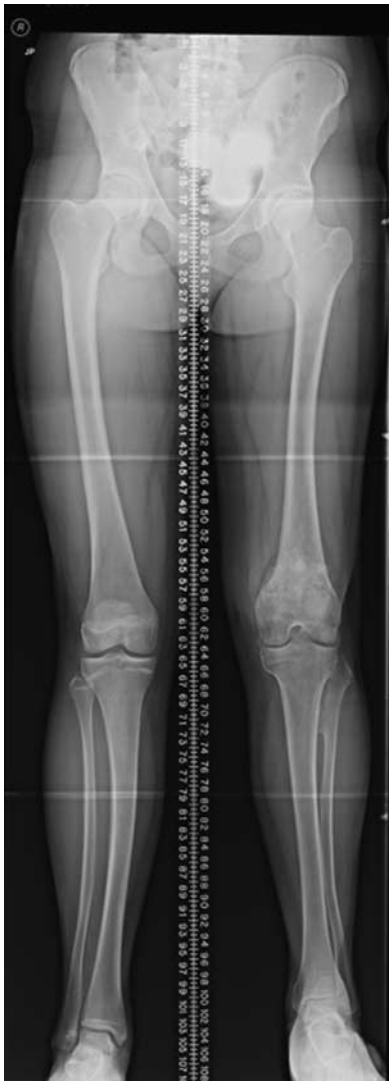

FIGURE 5. Patient PS101.3's standing anteroposterior view (age, 14.3 y). Of note is the 5.0 cm leg-length discrepancy. However, the hips are nearly level due to overgrowth of the left foot and marked cerebriform connective tissue nevus on the same side. This highlights the challenge of achieving equal leg lengths in patients with Proteus syndrome.

scanograms, but with the development of the picture archiving and communication system (PACS), we were better able to include leg measurements from the iliac crest to the floor. Unfortunately, for some of the tallest children, we had to use the older scanogram techniques because the PACS system could not accommodate their extreme height. Thus, radiographic measurement of LLD in this report is primarily limited to the long bones, which does not always accurately depict the entire clinical picture. For example, Figure 5 is a standing anteroposterior view of patient PS101.3. The image demonstrates an almost 5.0 cm overcorrection if one only considers the long bones; however, her pelvis is well-balanced due to significant overgrowth of the ipsilateral foot and pelvis. We have begun to adopt the MAP method: "Measure the leg-length discrepancy…Analyze the length of the 4 individual bone segments…(and) Pick the shortened bone segment."[17] This method evaluates the entire leg, including the hips, to identify where the length asymmetry is located and therefore where intervention should be targeted. The method allows better inclusion and evaluation of foot and pelvis. Results from this method need careful review, as the plantar cerebriform connective tissue nevus present in many patients may interfere with accurate measurement because it is composed of soft tissue and appreciated less well on x-ray and must be taken into consideration for overall limb length. Finally, our sample size did not permit controlled comparisons of intervention timing, methodology, or age across groups.

As this was not a controlled trial, we cannot prove that the interventions presented here were safe and effective. However, we systematically collected data on 8 patients with a diagnosis of PS, and we showed improvement in the LLD for all individuals. Ultimately, orthopaedic management in children with PS is a balancing act. Patients with PS can have many complications of the disease, a number of which may be life threatening, so minimizing the total number of interventions is essential. If the LLD becomes too severe (eg, PS73.3), it can be difficult to achieve equal leg lengths and the children may require large shoe lifts, which can interfere with their balance. Thus, early diagnosis of PS, regular clinical follow-up, and early initiation of guided growth interventions may improve outcomes. A high risk of DVT and PE remains a serious concern when planning for surgery in these patients. In this case series, DVT prophylaxis, sequential compression devices, rapid mobilization, and early initiation of physical therapy were used to support patient safety.

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