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Short stature as a presenting symptom of attenuated Mucopolysaccharidosis type I: case report and clinical insights

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Abstract

Background: Mucopolysaccharidosis type I (MPS I) results in significant disease burden and early treatment is important for optimal outcomes. Recognition of short stature and growth failure as symptoms of MPS I among pediatric endocrinologists may lead to earlier diagnosis and treatment.

Case presentation: A male patient first began experiencing hip pain at 5 years of age and was referred to an endocrinologist for short stature at age 7. Clinical history included recurrent respiratory infections, sleep apnea, moderate joint contractures, mild facial dysmorphic features, scoliosis, and umbilical hernia. Height was more than −2 SD below the median at all time points. Growth velocity was below the 3rd percentile. Treatment for short stature included leuprolide acetate and recombinant human growth hormone. The patient was diagnosed with MPS I and began enzyme replacement therapy with laronidase at age 18.

Conclusions: The case study patient had many symptoms of MPS I yet remained undiagnosed for 11 years after presenting with short stature. The appropriate path to MPS I diagnosis when patients present with short stature and/or growth failure plus one or more of the common signs of attenuated disease is described. Improved awareness regarding association of short stature and growth failure with attenuated MPS I is needed since early identification and treatment significantly decreases disease burden.

Keywords: MPS I diagnosis, MPS I signs and symptoms, Growth delay, Physician awareness, Early diagnosis, Short stature
history of MPS I patients, approximately 20% of a population of 60 patients with attenuated MPS I had delays of 5 years or longer in diagnosis, and consulted between 4 and 5 specialists before receiving an MPS I diagnosis [25]. Similarly, for 18 patients with MPS I (13 of whom had attenuated disease) whose symptoms were noted at 18 months, the mean age at biochemical diagnosis was 75 months [26]. While pilot programs for MPS I NBS are in progress around the world [27], they are not universally available, and diagnostic delay persists. There has been no significant improvement in reducing the delay in diagnosis of MPS I as of 2017 [28]. Thus, it remains likely that children with undiagnosed MPS I will be referred to specialists, including endocrinologists, for their care, and awareness of the early clinical signs and symptoms remains important.

Table 1: Common presenting/early symptoms in patients with attenuated MPS I [24, 51]

- Growth delay (normal birth weight, but growth failure or short stature)
- Joint contractures (primarily in hands/claw hand deformity), joint pain and stiffness, restricted mobility
- Carpal tunnel syndrome (trigger digits)
- Recurrent hernias (umbilical and/or inguinal)
- Corneal clouding
- Hepatosplenomegaly
- Skeletal abnormalities/dysostosis multiplex (e.g., kyphosis, scoliosis, hip dysplasia, flattened vertebral bodies, ear-shaped ribs, short thickened clavicles, bullet-shaped phalanges, dysplastic femoral heads, flattened acetabula, coxa valga and genu valgum deformities)
- Ear/nose/throat symptoms (recurrent ear infections, noisy breathing, sleep apnea, enlarged tongue, hearing loss)
- Heart murmur (valve abnormalities)
- Surgical history of multiple hernia repairs, PE tubes, tonsillectomy, adenoidectomy

All symptoms may not be present in the same patient, but are usually progressive. See Fig. 2 for the path to diagnosis.
diagnosis of MPS I. The patient began ERT with laronidase (0.58 mg/kg/week) at age 18.

Discussion and conclusions
The case study demonstrates that endocrinologists may not consider MPS I in cases of short stature, even when there are signs and symptoms suggestive of MPS I. Red-flag signs and symptoms for attenuated MPS I (Table 1) exist in the absence of parameters indicating juvenile idiopathic arthritis [39, 40]. The case presentation highlights the diagnostic journey of a patient with attenuated MPS I and short stature followed for over 10 years in a pediatric endocrinology clinic. A strength of this case is the duration of care and longitudinal growth data, although in some instances, assessments and clinical management information were unavailable. This patient had many of the signs and symptoms of attenuated MPS I, yet was not diagnosed until nearly 11 years after presenting to the pediatric endocrinologist with short stature. While not all of the signs listed in Table 1 may be apparent at the initial patient presentation to the endocrinologist, they are likely to develop over time when untreated, or be documented in patient clinical records and history. It is important to note that assessment of bone age in children with growth delay is typically done with an X-ray of the left hand and wrist; thus, pediatric endocrinologists are ideally situated to identify early phalangeal abnormalities (i.e., bullet shaped phalanges) typical of MPS I. A path to MPS I diagnosis when indicating signs are present is shown in Fig. 3.

### Table 2: Timeline of assessments, diagnoses and treatment

| Patient age | Symptom(s) | Assessments/diagnoses | Treatment(s) |
|-------------|------------|------------------------|--------------|
| 5–7 years   | Hip pain, recurrent respiratory infections | Orthopedist assessment and diagnosis of bilateral Legg-Calve-Perthes disease | unknown |
| 7–18 years  | Short stature: see Figs. 1 and 2 | Pediatric endocrinologist assessment | Leuprolide acetate (3.75 mg/month) ages 13–16 Growth hormone (0.1IU/kg/day) ages 14–18 |
| 18 years    | Short stature, moderate joint contractures, mild facial dysmorphic features (coarsening of features), scoliosis, and an umbilical hernia | Referred to metabolic disease center by treating pulmonologist, enzyme activity screening for MPS I positive; genetic analysis positive for MPS I | Enzyme replacement therapy with laronidase (weekly 0.58 mg/kg infusions) initiated |

**Fig. 1** Longitudinal Growth for Patient with Attenuated MPS I from Case Study. Height of case study patient by age is shown by the blue markers with timing and duration of leuprolide acetate, growth hormone and laronidase treatments indicated. WHO Child Growth Standards are indicated.
There is considerable overlap of presenting symptoms among the MPS disorders, therefore, screening identified in Fig. 3 should take into account other MPS disorders where short stature is common. Upon consideration of an MPS disorder, a urine GAG (uGAG) test (that may include analyses to determine abnormal GAG pattern, such as electrophoresis or tandem mass spectrometry) can determine the presence of lysosomal storage material. Results of the uGAG test as indicated in Fig. 3 can warrant referral to a geneticist or metabolic disease specialist, who can initiate appropriate enzyme and genetic testing to confirm or rule out an MPS diagnosis. Several
barriers can exist for appropriate referrals of pediatric patients to metabolic specialists and geneticists, including cost and insurance, wait times, and location [41, 42] and improvements in accessibility for lysosomal storage disease assays may be needed [43]. Studies suggest that increased awareness for endocrinologists may be helpful to highlight the possibility of attenuated MPS in patients presenting with short stature [37, 38]. In a retrospective assessment of outpatient medical records of patients with short stature of unknown etiology in a pediatric endocrinology service, follow-up screening of 23 patients revealed previously undiagnosed MPS in 3 patients [37]. In another study, 135 physicians with expertise in pediatrics and endocrinology from seven countries (United States, Canada, Italy, Germany, Spain, Mexico, and Brazil) participated in a blinded review of cases for pediatric or adolescent patients with MPS I [38]. Depending on the case reviewed, only 22% to 58% of physicians took steps towards a correct MPS I diagnosis. Juvenile idiopathic arthritis was the most common incorrect diagnosis made. A key distinction in the diagnosis of MPS I is the absence of biochemical parameters diagnostic of juvenile idiopathic arthritis. While algorithms exist that include MPS I in the differential diagnosis of juvenile arthritis for pediatric rheumatologists [39, 40], growth specialists and endocrinologists may be among the physicians encountering individuals with undiagnosed MPS disorders, and similar guidelines could prove helpful for recognizing the red-flag signs and symptoms of MPS I and other MPS disorders. A proposed algorithm that includes short stature as a presenting sign in attenuated MPS I has recently been published [44].

The mechanism behind short stature in patients with MPS I is not completely known, but is most likely a secondary characteristic resulting from structural, metabolic, and endocrine abnormalities. Structurally, skeletal abnormalities limit longitudinal growth and final height, but alone cannot explain short stature in patients with MPS I. Pituitary and thyroid dysfunction, GHD, precocious puberty, and pubertal failure have all been reported in patients with MPS I [32, 45]. However, it is important to note that in the absence of GHD, hGH treatment of patients with MPS I has not been proven to be effective.

Enzyme replacement therapy with laronidase has resulted in increased growth velocity in pediatric patients [46], particularly in prepubescent children with MPS I [20]. In sibling studies, improved musculoskeletal outcomes were noted in the younger sibling who began ERT in infancy [5, 18, 19]. Retrospective studies indicate that early initiation of laronidase can stabilize existing skeletal disease, and prevent or delay clinical manifestations if initiated prior to symptom onset [5, 19–22]. Patients with attenuated MPS I that were less than 10 years of age at treatment initiation remained closer to age-matched norms for several disease parameters, including height, compared with patients that were ≥ 10 years of age at the start of treatment [22]. There is disagreement regarding the benefits of administration of recombinant human growth hormone, and this is an area of active study [47].

In summary, short stature is a common presenting sign of attenuated MPS I, and may be the symptom that drives clinical care in these patients [36, 48, 49]. Since pediatric endocrinologists are typically the first physician to whom patients with short stature are referred [35], they can play a pivotal role in improving the health and quality of life of patients with attenuated MPS I. Early diagnosis of MPS I and initiation of treatment is critically important as it improves patient outcomes and reduces disease burden [5, 6, 8, 19, 22]. MPS I should be considered in any patient with short stature and/or growth failure plus one or more of the common signs described in Table 1. The path to diagnosis (Fig. 2) includes urine GAG test, referral to geneticist (or metabolic disease specialist), and appropriate enzyme and genetic testing. Improving the ability of pediatric endocrinologists to recognize the disease manifestations of MPS I can lead to earlier diagnosis and treatment for individuals with MPS I.

Abbreviations
GAG: Glycosaminoglycans; GHD: Growth hormone deficient; hGH: Human growth hormone; HSCT: Hematopoietic stem cell transplant; IDUA: α-L-iduronidase; MPS I: Mucopolysaccharidosis type I; uGAG: Urinary glycosaminoglycans

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De-identified patient data are available upon request.

Authors’ contributions
AMM and SK provided patient data; LP, KL, AMM and SK were involved in analyzing and interpreting data; MVNR and NT initiated the study, and all authors participated in manuscript development and writing. All authors read and approved the final manuscript.

Author’s information
Not applicable.

Ethics approval and consent to participate
The Universidade Federal de São Paulo, Ethics Committee, São Paulo, Brazil provided approval for use of the case study medical records for retrospective studies (CEP-UNIFESP #0007/11).

Consent for publication
The patient, who was over 18 at the time of manuscript preparation, provided written consent for use of data in the publication.
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References

1. Muenzer J. Overview of the mucopolysaccharidoses. Rheumatology (Oxford). 2012;50(Suppl 5):v4–12.
2. Moore D, Connock MJ, Wraith E, Lavery C. The prevalence of and survival in published maps and institutional affiliations. Orphanet J Rare Dis. 2008;3:24–30.
3. Neufeld E, Muenzer J. The mucopolysaccharidoses. In: Schriver C, Beaudet A, Sly W, Valle D, Childs B, skolnick TT, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill; 2001. p. 3421–52.
4. Thomas JA, Beck M, Clarke JT, Cox GF. Childhood onset of Scheie syndrome, the attenuated form of mucopolysaccharidosis I. J Inherit Metab Dis. 2010;33(4):421–7.
5. Al-Sannaa NA, Bay L, Barbouth DS, Benhayoun Y, Goizet C, Guelbert N, et al. Early initiation of enzyme replacement therapy for the attenuated form of mucopolysaccharidosis I: the important role of early treatment. BMC Med Genet. 2016;17(1):19.
6. D’Aco K, Underhill L, Rangachari L, Arn P, Cox GF, Giugliani R, et al. Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I registry. Eur J Pediatr. 2012;171(6):911–9.
7. de Ru MH, Boelens JJ, Das AM, Jones SA, van der Lee JH, Mahlaoui N, et al. Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with mucopolysaccharidosis type I: results of a European consensus procedure. Orphanet J Rare Dis. 2011;6:55–62.
8. Gabrielli O, Clarke LA, Bruni S, Coppa GV. Enzyme-replacement therapy in a 5-month-old boy with attenuated presumptomatic MPS I 5-year follow-up. Pediatrics. 2009;123(1):e183–7.
9. Gabrielli O, Clarke LA, Ficcadenti A, Santoro L, Zampini L, Volpi N, et al. 12 year follow up of enzyme-replacement therapy in two siblings with attenuated mucopolysaccharidosis I: Experience in three siblings. Mol Genet Metab. 2013;109(3):315–6.
10. Laraway S, Wraith JE, Beck M, Jones S, Wraith JE. Does early use of enzyme replacement therapy alter the natural history of mucopolysaccharidosis I? Experience in three siblings. Mol Genet Metab. 2016;139(3):315–6.
11. Vieira T, Schwartz I, Munoz V, Pinto L, Steiner C, Ribeiro M, et al. Mucopolysaccharidoses in Brazil: what happens from birth to biochemical diagnosis? Am J Med Genet A. 2008;146A(13):1741–7.
12. Parni R, Broomfield A, Cleary MA, De Meiflcr L, Di Rocco M, Fatihala WM, et al. International working group identifies need for neonborn screening for mucopolysaccharidosis type I but states that existing hurdles must be overcome. Acta Paediatr. 2018.
13. Kuiper GA, Meijer OLM, Langereis EJ, Wijburg FA. Failure to shorten the diagnostic delay in two ultra-orphan diseases (mucopolysaccharidoses types I and III): potential causes and implications. Orphanet J Rare Dis. 2018;3(1):12.
14. Morishita K, Petty RE. Musculoskeletal manifestations of mucopolysaccharidoses. Rheumatology (Oxford). 2011;50(Suppl 5):v19–25.
15. Rozycka-Swiatkowska A, Jurecka A, Cieslik J, Tylki-Szymanska A. Growth patterns in children with mucopolysaccharidosis I and II. World J Pediatr. 2015;11(3):226–31.
16. Tylki-Szymanska A, Rozycka A, Jurecka A, Marucha J, Czartoryska B. Anthropometric data of 14 patients with mucopolysaccharidosis I: retrospective analysis and efficacy of recombinant human alpha-L-iduronidase (laronidase). Mol Genet Metab. 2009;99(1):10–7.
17. Polgreen LE, Miller BS. Growth patterns and the use of growth hormone in the mucopolysaccharidoses. J Pediatr Rehabil Med. 2010;3(2):15–38.
18. Rogers DG, Nasomyont N. Growth hormone treatment in a patient with hurter-Scheie syndrome. J Pediatr Endocrinol Metab. 2014;27(9–10):957–60.
19. Bantow C, Renucha C. Evaluation of short and tall stature in children. Am Fam Physician. 2015;92(14):53–60.
20. Witt JM, Oostdijk W, Losekoot M, van Duvenvoorde HA, Ruivenkamp CA, Kant SG. Mechanisms In Endocrinology: novel genetic causes of short stature. Eur J Endocrinol. 2016;174(4):R415–73.
21. Ayuk A, Obu H, Ughasoro M, Ibezioke N. Untreating short stature in a possible case of mucopolysaccharidosis. Ann Med Health Sci Res. 2014;4(Suppl 1):S38–42.
22. Franco J, Espinosa G, Garcia F. Screening for mucopolysaccharidosis in patients with short stature of unknown etiology. Mgmt. 2016;17:547.
23. Thibault N, Cabral JM, Munoz Rojas MV, Bruni S. Awareness of MPS I Among Pediatric Endocrinologists. 14th International Symposium on MPS and Related Disorders; July 14–17; Bonn, Germany 2016.
39. Cimaz R, Coppa GV, Kone-Paut I, Link B, Pastores GM, Elorduy MR, et al. Joint contractures in the absence of inflammation may indicate mucopolysaccharidosis. Pediatr Rheumatol Online J. 2009;7:18–25.

40. Cimaz R, Vijay S, Haase C, Coppa GV, Bruni S, Wraith E, et al. Attenuated type I mucopolysaccharidosis in the differential diagnosis of juvenile idiopathic arthritis: a series of 13 patients with Scheie syndrome. Clin Exp Rheumatol. 2006;24(2):196–202.

41. Delikurt T, Williamson GR, Anastasiadou V, Skilton H. A systematic review of factors that act as barriers to patient referral to genetic services. Eur J Hum Genet. 2015;23(6):739–45.

42. Beene-Harris RY, Wang C, Bach JV. Barriers to access: results from focus groups to identify genetic service needs in the community. Community Genet. 2007;10(1):10–8.

43. Verma J, Thomas DC, Kasper DC, Sharma S, Puri RD, Bijarnia-Mahay S, et al. Inherited Metabolic Disorders: Efficacy of Enzyme Assays on Dried Blood Spots for the Diagnosis of Lysosomal Storage Disorders. JIMD Rep. 2016.

44. Tylki-Szymanska A, De Meirleir L, Di Rocco M, Fathalla WM, Guffon N, Lampe C, et al. Easy-to-use algorithm would provide faster diagnoses for mucopolysaccharidosis type I and enable patients to receive earlier treatment. Acta Paediatr. 2018;107(8):1402–8.

45. Gardner CJ, Robinson N, Meadows T, Wynn R, Will A, Mercer J, et al. Growth, final height and endocrine sequelae in a UK population of patients with huerler syndrome (MPS1H). J Inherit Metab Dis. 2011;34(2):489–97.

46. Kakas ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med. 2001;344(3):182–8.

47. Polgreen LE, Thomas W, Orchard PJ, Whitey CB, Miller BS. Effect of recombinant human growth hormone on changes in height, bone mineral density, and body composition over 1-2 years in children with huerler or hunter syndrome. Mol Genet Metab. 2014;111(2):101–6.

48. Clarke LA, Hollak CE. The clinical spectrum and pathophysiology of skeletal complications in lysosomal storage disorders. Best Pract Res Clin Endocrinol Metab. 2015;29(2):219–35.

49. Gadve SS, Sarma D, Saikia UK. Short stature with umbilical hernia - not always due to cretinism: a report of two cases. Indian J Endocrinol Metab. 2012;16(3):453–6.

50. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for north American children. J Pediatr. 1985;107(3):317–29.

51. Pastores GM, Arn P, Beck M, Clarke JT, Guffon N, Kaplan P, et al. The MPS I registry: design, methodology, and early findings of a global disease registry for monitoring patients with Mucopolysaccharidosis type I. Mol Genet Metab. 2007;91(1):37–47.