Mucopolysaccharidosis I (MPS I)

Contents

Mucopolysaccharidosis I consists of three clinical entities with varying degrees of clinical manifestations, all due to the same lysosomal enzyme deficiency, α-L-iduronidase. Hurler (MPS I-H) and Scheie (MPS I-S) syndromes represent phenotypes at the two ends of the clinical spectrum; the Hurler–Scheie syndrome (MPS I-H/S) represents a phenotype of intermediate clinical severity. In most instances, the subtype of MPS I can only be assigned on the basis of clinical criteria, including the rate of progression of symptoms. The incidences for MPS I-H, MPS I-H/S, and MPS I-S are estimated to be 1/76,000–1/144,000, 1/280,000, and 1/840,000–1/1,300,000 live births, respectively.

Synonyms and Related Disorders

α-L-Iduronidase deficiency; Hurler (MPS I-H); Hurler–Scheie (MPS I-H/S); Scheie (MPS I-S) syndromes

Genetics/Basic Defects

1. Inheritance: autosomal recessive
2. The *IDUA* gene (Scott et al. 1990)
   1. Localized to chromosome 4p16.3, close to the Huntington disease gene
   2. Spans 19 kb including 14 exons
3. Caused by mutations in the α-L-iduronidase (*IDUA*) gene (Scott et al. 1992, 1993, 1995; Lee-Chen et al. 1999)
   1. Two major alleles (W402X and Q70X) (Bunge et al. 1994; Beesley et al. 2001) and a minor allele (P533R) accounting for over half the MPS I alleles in the Caucasian population.
   2. No functional enzymes produced by above-mentioned alleles, giving rise to the severe form of α-L-iduronidase deficiency (MPS I-H).
   3. Limited mutations expected to cause the attenuated clinical phenotypes of MPS I-S or MPS I-H/S.
   4. One of the mutations resulting in Scheie syndrome is a base substitution in intron 7 that creates a new splice site and produces a frameshift. Since the old splice site is not obliterated, some normal enzymes still can be made to overcome the worst features of MPS I.
   5. Most other alleles that lead to MPS I-S or MPS I-H/S carry missense mutations (Lee-Chen and Wang 1997).

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6. In the Japanese population studied, MPS I-H/S results from compound heterozygosity of two mutations (704ins5 and R89Q), which, in homozygous form, would give rise to MPS I-H and MPS I-S, respectively (Yamagishi et al. 1996).

4. Genotype–phenotype correlations
   1. General principle (McKusick et al. 1972; Mueller et al. 1984)
      1. Any combination of two severe alleles leads to severe MPS I. A severe allele is one that produces the severe phenotype in either the homozygous state or compound heterozygous state.
      2. Intermediate and mild MPS I: usually associated with one severe allele and another allele that permits production of some residual enzyme activity.
   2. Alleles associated with severe phenotype
      1. Two common severe mutations (W402X and Q70X) always confer a severe phenotype whether present in a homozygous state or in a compound heterozygous state.
      2. Additional mutations (474-2a-g, A327P, P533R, A75T, L218P).
   3. Alleles associated with mild phenotype
      1. 678-7a-g
      2. R89Q
5. Pathophysiology
   1. Underlying molecular defect leads to a loss or marked reduction in α-L-iduronidase (*IDUA*), a lysosomal enzyme involved in the degradation of glycosaminoglycans heparan sulfate and dermatan sulfate.
   2. Because of the enzyme deficiency, excessive accumulation of acid mucopolysaccharides (glycosaminoglycans) in the tissue occurs, leading to a wide effect on various systems and remarkable changes in the morphogenesis.

Clinical Features

1. Hurler syndrome (MPS I-H)
   1. General clinical characteristics
      1. The prototype of MPS representing the severe end of clinical spectrum
      2. A progressive disorder with multiple organ and tissue involvement, leading to death in childhood
      3. Normal phenotype at birth and in early infancy but deteriorates progressively afterward
      4. Diagnosis usually made between 4 and 18 months of age
      5. Short stature (linear growth stops at 2–3 years of age)
      6. Developmental delay by age 12–24 months, with a maximum functional age at the level of 2–4 years, followed by progressive mental deterioration
   2. Coarse facial features (one of the earliest signs)
      1. Ocular hypertelorism
      2. Prominent eyes
      3. Bushy eyebrows
      4. Depressed nasal bridge
      5. Wide nostrils
      6. Large and thickened lips
      7. Large tongue
      8. Hypertrophy of the gum and the bony alveolar ridge
   3. Other craniofacial features
      1. A large scaphocephalic head with frontal bossing.
      2. Communicating hydrocephalus common after age 2–3 years. Shunting procedures may be beneficial for relieving increased intracranial pressure for some children.
      3. Noisy breathing with persistent nasal discharge (chronic rhinorrhea).
      4. Upper respiratory and ear infections.
   4. Ophthalmologic features
      1. Progressive clouding of the cornea (the hallmark of the syndrome) beginning at the first year of life, leading to impaired vision
      2. Open-angle glaucoma
      3. Retinal degeneration resulting in decreased peripheral vision
      4. Night blindness
   5. Auditory features
      1. Frequent sensorineural or mixed deafness

2. Contributing factors:
    1. Frequent middle ear infection from Eustachian tube dysfunction, caused by storage of glycosaminoglycans within the oropharynx
    2. Dysostosis of the ossicles of the middle ear
    3. Scarring of the tympanic membrane
    4. Damage to the eighth nerve
6. Cardiovascular features
    1. Cardiac valvular disease resulting from storage of mucopolysaccharide in the mitral, aortic, tricuspid, or pulmonary valves, leading to congestive heart failure.
    2. Thickened coronary artery valves, leading to angina pectoris and myocardial infarction.
    3. Possible fatal cardiomyopathy as a presenting feature for some MPS I infants less than 1 year old. Endocardial fibroelastosis has been noted postmortem in these patients.
    4. Aortic stenosis and uncontrolled hypertension (Taylor et al. 1991; Eakins and Kan 2010): although uncommon, aortic stenosis should be included in the differential diagnoses in children with Hurler syndrome and poorly controlled hypertension.
7. Gastrointestinal features
    1. Protuberant abdomen
    2. Progressive hepatosplenomegaly
8. Skeletal abnormalities: dysostosis multiplex
    1. Short neck
    2. Characteristic kyphoscoliosis when attempting to sit
    3. Ultimate frank gibbus deformity
    4. Stiff joints with limited mobility
    5. Claw hands (flexed stubby fingers and broad hands)
9. Connective tissue abnormalities
    1. Inguinal and umbilical hernias: common findings and usually present at birth
    2. Thick skin
10. Prognosis
    1. Bedridden before the end of the juvenile period
    2. Early demise prior to 10 years of age
    3. Usual causes of death
        1. Obstructive airway disease (Shapiro et al. 1985)
        2. Respiratory infection
        3. Cardiac complications

2. Scheie syndrome (MPS I-S)
    1. The mildest form of MPS I
    2. Normal stature
    3. Normal intelligence
    4. Onset of significant signs usually after 5 years
    5. Diagnosis commonly made between 10 and 20 years of age
    6. Coarse facial features
    7. Deafness in some patients
    8. Joint stiffness
        1. Claw hands
        2. Stiff painful foot
    9. Carpal tunnel syndrome
    10. Pes cavus
    11. Genu valgum
    12. Ocular manifestations
        1. Corneal clouding
        2. Glaucoma
        3. Retinal degeneration
    13. Aortic valvular disease (stenosis and regurgitation due to mucopolysaccharide deposits in the valves and chordae tendineae)
    14. Obstructive airway disease with sleep apnea in some patients
    15. Mild hepatosplenomegaly
    16. Mild dysostosis multiplex
    17. Less common pachymeningitis cervicalis (compression of the cervical cord by thickened dura) than MPS I-H/S
    18. Potential normal life span
3. Hurler–Scheie compound (MPS I-H/S)
    1. Clinical phenotype intermediate between Hurler and Scheie syndromes (Kajii et al. 1974; Kaibara et al. 1979)
    2. Progressive somatic involvement, including dysostosis multiplex, with little or no intellectual dysfunction

3. Age of onset: usually between 3 and 8 years
4. Survival to adulthood: common
5. Deafness
6. Craniofacial features
    1. Coarse facial features: less obvious
    2. Micrognathia in some patients
    3. Broad mouth
    4. Square jaw
    5. Short neck
7. Ophthalmologic features
    1. Corneal clouding in all patients
    2. Glaucoma
    3. Retinal degeneration
    4. Optic atrophy
8. Valvular heart disease (mitral valve insufficiency) developing by the early to mid-teens
9. Skeletal features
    1. Short stature
    2. Small thorax
    3. Severe joint involvement (stiffness)
    4. Kyphoscoliosis
    5. Back pain
    6. Characteristic claw hand deformity
    7. Carpal tunnel syndrome
10. Gastrointestinal features
    1. Varying degrees of hepatomegaly
    2. Hernias
11. Pachymeningitis cervicalis (compression of the cervical cord due to mucopolysaccharide accumulation in the dura)
12. Communicating hydrocephalus uncommon in patients who have normal intelligence
13. Spondylolisthesis of the lower spine, leading to spinal cord compression
14. Causes of death (age around teens and 20s)
    1. Upper airway obstruction
    2. Cardiac involvement

Diagnostic Investigations

1. Developmental assessment
2. Ophthalmologic examination
3. ECG and echocardiography for cardiovascular status (Nelson et al. 1990)
4. Cranial ultrasound for hydrocephalus
5. Skeletal survey
    1. Dysostosis multiplex
    2. Skull
        1. Large, thickened calvarium
        2. Premature closure of lambdoidal and sagittal sutures
        3. Shallow orbits
        4. Enlarged J-shaped sella
        5. Abnormally spaced teeth with dentigerous cysts
    3. Ribs
        1. Oar shaped and narrowed at the vertebral ends
        2. Flat/broad at the sternal ends
    4. Vertebra
        1. Beaked anteriorly (anterior hypoplasia) of lumbar vertebrae with kyphosis (an early sign)
        2. Scalloped posteriorly
        3. Thoracolumbar gibbus, resulting from anterior wedging of the vertebrae
        4. Hypoplasia of the odontoid, leading to atlantoaxial subluxation
    5. Pelvis
        1. Poorly formed pelvis
        2. Small femoral heads
        3. Coxa valga
    6. Long bones
        1. Widened diaphysis of the long bones
        2. Lack of normal modeling and tabulation
        3. Irregular metaphysis
        4. Poorly developed epiphyseal centers
        5. Distal ends of the radius and ulna angulate toward each other
        6. Claw hands
        7. Thickened and bullet-shaped phalanges
        8. Coarsening of the trabeculae of the phalanges and metacarpals
        9. Proximal narrowing of the metacarpals
        10. Marked irregularity and retarded ossification of the carpal bones
    7. Other bones
        1. Short, thickened, and irregular clavicles
        2. Shortened and trapezoid-shaped phalanges with widened diaphyses

6. Biochemical/molecular studies for MPS I-H, MPS I-HS, and MPS I-S
    1. Excessive urinary excretion of glycosaminoglycans (dermatan and heparan sulfates): a useful preliminary test
    2. Metachromatic staining of fibroblasts and leukocyte inclusions (nonspecific lab findings)
    3. Enzyme assay: deficient α-L-iduronidase in WBC, serum, cultured fibroblast, and CSF
    4. Accumulation of glycosaminoglycans in cultured fibroblasts correctable by uptake of α-L-iduronidase
    5. Mutation analysis or sequence analysis of *IUDA* gene: possible to identify both *IDUA* mutations in 95% of patients with MPS I
    6. Characterization of gene mutation: worthwhile for phenotype prediction and genetic counseling
7. Carrier testing
    1. Measurement of α-L-iduronidase enzyme activity: not a reliable method, requiring testing of obligatory carriers within the family first to determine if their levels of IDUA enzyme activity can be distinguishable from the normal
    2. Molecular genetic testing of *IUDA* to identify carriers among at-risk family members when both mutation alleles have been identified in an affected family member

Genetic Counseling

1. Recurrence risk
    1. Patient's sib: 25% chance of being affected
    2. Patient's offspring:
        1. MPS I-S: not increased unless the spouse is a carrier
        2. MPS I-H and MPS I-H/S: not surviving to reproductive age
2. Prenatal diagnosis from samples of CVS, amniocentesis, and fetal blood (Fratantoni et al. 1969; Ikeno et al. 1981; Muenzer 1986; Young 1992; Fensom and Benson 1994)
    1. Enzyme assays (deficient α-L-iduronidase) and increased level of ^{35}S-sulfate incorporation measured in cultured cells obtained from amniocentesis or CVS for pregnancy at risk
    2. Mutation analysis of the *IDUA* gene in fetal DNA extracted from cells obtained by CVS or amniocentesis if both mutant *IDUA* alleles have been identified in a previously affected sib or in the parents of the at-risk fetus
3. Preimplantation genetic diagnosis (PGD) for at-risk pregnancies: requires prior identification of both *IDUA* disease-causing mutations in the family
4. Management (Clarke and Heppner 2011; Muenzer and Fisher 2004)
    1. Supportive care
        1. Early infant stimulation programs
        2. Eye care: corneal transplantation successful but donor grafts eventually becoming cloudy
        3. Range of motion exercises to preserve joint function
        4. Physical therapy
    2. Orthopedic surgery (Peters et al. 1998; Van Heest et al. 1998)
        1. Surgical decompression of the median nerve for carpal tunnel syndrome resulting in various restorations of motor hand activity
        2. Trigger digits
        3. Genu valgum
        4. Kyphoscoliosis
        5. Acetabular dysplasia
        6. Atlantooccipital stabilization
    3. Ventriculoperitoneal shunting for hydrocephalus
        1. Generally palliative
        2. May improve quality of life
    4. Tracheotomy or high-pressure continuous positive airway pressure with supplemental oxygen
    5. Tonsillectomy and adenoidectomy to correct Eustachian tube dysfunction and to decrease upper airway obstruction
    6. Cardiovascular care
        1. Bacterial endocarditis prophylaxis

2. Valve replacement surgery
3. Management of severe dilated cardiomyopathy: enzyme replacement therapy pre-transplant can improve cardiac function sufficiently to permit safe allogenic hematopoietic stem cell transplantation using myeloablative conditioning (Wiseman et al. 2013)
7. Surgical repair of inguinal hernias
8. Early surgical intervention to prevent severe complications from progressive compression of the spinal cord
9. Major anesthetic risks exhibited by patients with MPS I (Walker et al. 1994; Moores et al. 1996)
    1. Avoid hyperextension of the neck since dysostosis multiplex can lead to instability of the spine including the atlantoaxial joint.
    2. Difficulty in induction of anesthesia due to inability to maintain an adequate airway.
    3. Require fiberoptic laryngoscopy for intubation.
    4. Slow recovery from anesthesia.
    5. Common postoperative airway obstruction.
10. Allogenic bone marrow transplantation from an unaffected, HLA-compatible donor (Peters et al. 1996, 1998; Guffon et al. 1998)
    1. Beneficial effect: replacement of deficient macrophages by marrow-derived donor macrophages to provide ongoing source of normal enzyme capable of gaining access to the various sites of storage.
    2. Slows the course of cognitive decline if the therapy starts before the developmental delay is evident.
    3. Improves survival (Whitley et al. 1993), reducing facial coarseness, hepatosplenomegaly, hearing, and normal cardiac function.
    4. Skeletal manifestations (Vellodi et al. 1997) and corneal clouding continue to progress despite successful transplantation. Surgeries will be required for the persistent orthopedic problems.
    5. Significantly limited by the availability of donors. The immunosuppressive therapy for the prevention of rejection carries significant toxicity.
    6. The procedure of the transplantation carries a high risk of morbidity and mortality. Failure to achieve stable engraftment and development of graft-versus-host disease is a significant barrier to successful bone marrow transplantation for many children.
    7. Hematopoietic stem cell transplantation: the treatment of choice for a child with Hurler syndrome who is younger than 2 years of age and has minimal or no central nervous system disease (Muenzer 2004).
11. Cord blood transplantation (Staba et al. 2004)
    1. Use cord blood transplants from partially HLA-matched, unrelated donors.
    2. Donors readily available.
    3. An excellent source of stem cells for transplantation.
    4. Sustained engraftment can be achieved without total-body irradiation in young children.
    5. Low incidence for acute graft-versus-host disease (GVHD).
    6. Absence of extensive chronic GVHD.
    7. As effective as bone marrow transplantation.
    8. Unrelated umbilical cord blood transplantation was associated with improved somatic disease and neurodevelopment (Coletti et al. 2015).
12. Enzyme replacement therapy (ERT) (Kakkis et al. 2001; Kakkis 2002)
    1. An etiology-specific treatment that seeks to address the underlying

pathophysiology of MPS I by delivering sufficient IDUA activity to reverse and prevent glycosaminoglycan accumulation (Wraith et al. 2004)

2. Effectiveness depending on the ability of recombinant enzymes injected intravenously to enter cells and localize to the lysosome, the appropriate intracellular site
3. Use of recombinant human α-L-iduronidase (laronidase: Aldurazyme)
    1. Aldurazyme®: currently licensed in the USA, Europe, and Canada for use in treating non-CNS manifestations of MPS I. The current dose regime involves premedication with an anti-inflammatory and antihistamine drugs and intravenous weekly infusion of 100 U/kg of Aldurazyme® over 4 h (Clarke and Heppner 2011).
    2. Significant reduction in liver size.
    3. Increase in height and weight.
    4. Decrease in joint restriction.
    5. Improvement in breathing (respiratory function) and sleep apnea.
    6. Decreased glycosaminoglycan storage.
    7. Improvements in cardiopulmonary function, airway obstruction, and joint mobility in Hurler–Scheie syndrome (nonneuronopathic MPS I) (Bijarnia et al. 2009).
    8. Recommended for patients with milder or attenuated forms of MPS I. Infusions of recombinant enzyme are a safer alternative for treating the somatic disease and improving the quality of life of such patients. An intravenously administered enzyme is not expected to cross the blood–brain barrier and affect central nervous system disease (Muenzer 2004).
    9. Enzyme replacement therapy with laronidase can be used with pre- and peri-hematopoietic stem cell transplant, which is now the gold standard treatment in those patients diagnosed under 2.5 years of age (Jameson et al. 2013).
13. Hematopoietic stem cell transplantation (HSCT) (Bijarnia et al. 2009): treatment of choice for children <2 years of age with MPS I-H who have minimal or no central nervous disease
14. Combination of ERT followed by HSCT in neuronopathic Hurler syndrome
    1. Corrects the enzyme deficiency until endogenous enzyme production is established
    2. Reverses airway obstruction and cardiovascular complications, thus reducing mortality and morbidity at the time of transplant

References

Beesley, C. E., Meaney, C. A., Greenland, G., et al. (2001). Mutational analysis of 85 mucopolysaccharidosis type I families: Frequency of known mutations, identification of 17 novel mutations and in vitro expression of missense mutations. *Human Genetics, 109*, 503–511.

Bijarnia, S., Shaw, P., Vimpani, A., et al. (2009). Combined enzyme replacement and haematopoietic stem cell transplantation in Hurler syndrome. *Journal of Paediatrics and Child Health, 45*, 469–472.

Bunge, S., Kleijer, W. J., Steglich, C., et al. (1994). Mucopolysaccharidosis type I: Identification of 8 novel mutations and determination of the frequency of the two common alpha-L-iduronidase mutations (W402X and Q70X) among European patients. *Human Molecular Genetics, 3*, 861–866.

Clarke L. A., & Heppner, J. (2011). Mucopolysaccharidosis type I. *GeneReviews*. Retrieved 21 July 2011. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1162/

Coletti, H. Y., Aldenhoven, M., Yelin, K., et al. (2015). Long-term functional outcomes of children with Hurler syndrome treated with unrelated umbilical cord blood transplantation. *JIMD Reports, 20*, 77–88.

Eakins, C., & Kan, J. H. (2010). Uncontrolled hypertension in a child with Hurler syndrome. *Pediatric Radiology, 40*(Suppl 1), S120.

Fensom, A. H., & Benson, P. F. (1994). Recent advances in the prenatal diagnosis of the mucopolysaccharidoses. *Prenatal Diagnosis, 14*, 1–12.

Fratantoni, J. C., Neufeld, E. F., Uhlendorf, B. W., et al. (1969). Intrauterine diagnosis of the Hurler and Hunter syndromes. *The New England Journal of Medicine, 280*, 686–688.

Guffon, N., Souillet, G., Maire, I., et al. (1998). Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. *Journal of Pediatrics, 133*, 119–125.

Ikeno, T., Minami, R., Wagatsuma, K., et al. (1981). Prenatal diagnosis of Hurler's syndrome-biochemical studies on the affected fetus. *Human Genetics, 59*, 353–359.

Jameson, E., Jones, S., & Wraith, J. E. (2013). Enzyme replacement therapy with laronidase (Aldurazyme) for treating mucopolysaccharidosis type 1. *Cochrane Database of Systemic Reviews,* 11, 1–15.

Kaibara, N., Eguchi, M., Shibata, K., et al. (1979). Hurler-Scheie phenotype: A report of two pairs of inbred sibs. *Human Genetics, 53*, 37–41.

Kajii, T., Matsuda, I., Osawa, T., et al. (1974). Hurler/Scheie genetic compound (mucopolysaccharidosis IH/IS) in Japanese brothers. *Clinical Genetics, 6*, 394–400.

Kakkis, E. D. (2002). Enzyme replacement therapy for the mucopolysaccharide storage disorders. *Expert Opinion on Investigational Drugs, 11*, 675–685.

Kakkis, E. D., Muenzer, J., Tiller, G. E., et al. (2001). Enzyme-replacement therapy in mucopolysaccharidosis I. *The New England Journal of Medicine, 344*, 182–188.

Lee-Chen, G. J., & Wang, T. R. (1997). Mucopolysaccharidosis type I: Identification of novel mutations that cause Hurler/Scheie syndrome in Chinese families. *Journal of Medical Genetics, 34*, 939–941.

Lee-Chen, G. J., Lin, S. P., Tang, Y. F., et al. (1999). Mucopolysaccharidosis type I. Characterization of novel mutations affecting α-L-iduronidase activity. *Clinical Genetics, 56*, 66–70.

McKusick, V. A., Howell, R. R., Hussels, I. E., et al. (1972). Allelism, nonallelism and genetic compounds among the mucopolysaccharidoses. *Lancet, I*, 993–996.

Moores, C., Rogers, J. G., McKenzie, I. M., et al. (1996). Anaesthesia for children with mucopolysaccharidoses. *Anaesthesia and Intensive Care, 24*, 459–463.

Mueller, O. T., Shows, T. B., & Opitz, J. M. (1984). Apparent allelism of the Hurler, Scheie, and Hurler/Scheie syndromes. *American Journal of Medical Genetics, 18*, 547–556.

Muenzer, J. (1986). Mucopolysaccharidoses. *Advances in Pediatrics, 33*, 269–302.

Muenzer, J. (2004). The mucopolysaccharidoses: A heterogeneous group of disorders with variable pediatric presentations. *Journal of Pediatrics, 144*, S27–S34.

Muenzer, J., & Fisher, A. (2004). Advances in the treatment of mucopolysaccharidosis type I. *The New England Journal of Medicine, 350*, 1932–1934.

Nelson, J., Shields, M. D., & Mulholland, H. C. (1990). Cardiovascular studies in the mucopolysaccharidoses. *Journal of Medical Genetics, 27*, 94–100.

Peters, C., Balthazor, M., Shapiro, E. G., et al. (1996). Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood, 87*, 4894–4902.

Peters, C., Shapiro, E. G., Anderson, J., The Storage Disease Collaborative Study Group, et al. (1998). Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty- four children. *Blood, 91*, 2601–2608.

Scott, H. S., Ashton, L. J., Eyre, H. J., et al. (1990). Chromosomal localization of the human α-L-iduronidase gene (*IDUA*) to 4p16.3. *American Journal of Human Genetics, 47*, 802–807.

Scott, H. S., Guo, X. H., Hopwood, J. J., et al. (1992). Structure and sequence of the human α-L-iduronidase gene. *Genomics, 13*, 1311–1313.

Scott, H. S., Litjens, T., Nelson, P. V., et al. (1993). Identification of mutations in the alpha-L-iduronidase gene (IDUA) that cause Hurler and Scheie syndromes. *American Journal of Human Genetics, 53*, 973–986.

Scott, H. S., Bunge, S., Gal, A., et al. (1995). Molecular genetics of mucopolysaccharidosis type I: Diagnostic, clinical, and biological implications. *Human Mutation, 6*, 288–302.

Shapiro, J., Strome, M., & Crocker, A. C. (1985). Airway obstruction and sleep apnea in Hurler and Hunter syndromes. *Annals of Otology, Rhinology and Laryngology, 94*, 458–461.

Staba, S. L., Escolar, M. L., Poe, M., et al. (2004). Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *The New England Journal of Medicine, 350*, 1960–1968.

Taylor, D. B., Blaser, S. I., Burrows, P. E., et al. (1991). Arteriopathy and coarctation of the abdominal aorta in children with mucopolysaccharidosis: Imaging findings. *AJR. American Journal of Roentgenology, 157*, 819–823.

Van Heest, A. E., House, J., Krivit, W., et al. (1998). Surgical treatment of carpal tunnel syndrome and trigger digits in children with mucopolysaccharide storage disorders. *The Journal of Hand Surgery (America), 23*, 236–243.

Vellodi, A., Young, E. P., Cooper, A., et al. (1997). Bone marrow transplantation for mucopolysaccharidosis type I: Experience of two British centres. *Archives of Disease in Childhood, 76*, 92–99.

Walker, R. W., Darowski, M., Morris, P., et al. (1994). Anaesthesia and mucopolysaccharidoses. A review of airway problems in children. *Anaesthesia, 49*, 1078–1084.

Whitley, C. B., Belani, K. G., Chang, P. N., et al. (1993). Long-term outcome of Hurler syndrome following bone marrow transplantation. *American Journal of Medical Genetics, 46*, 209–218.

Wiseman, D. H., Mercer, J., Tylee, K., et al. (2013). Management of mucopolysaccharidosis type IH (Hurler's syndrome) presenting in infancy with severe dilated cardiomyopathy: A single institution's experience. *Journal of Inherited Metabolic Diseases, 36*, 263–270.

Wraith, J. E., Clarke, L. A., Beck, M., et al. (2004). Enzyme replacement therapy for mucopolysaccharidosis I: A randomized, double-blinded, placebo-controlled, multinational study of recombinant human a-L-iduronidase (laronidase). *Journal of Pediatrics, 144*, 581–588.

Yamagishi, A., Tomatsu, S., Fukuda, S., et al. (1996). Mucopolysaccharidosis type I: Identification of common mutations that cause Hurler and Scheie syndromes in Japanese populations. *Human Mutation, 7*, 23–29.

Young, E. P. (1992). Prenatal diagnosis of Hurler disease by analysis of alpha-iduronidase in chorionic villi. *Journal of Inherited Metabolic Disease, 15*, 224–230.

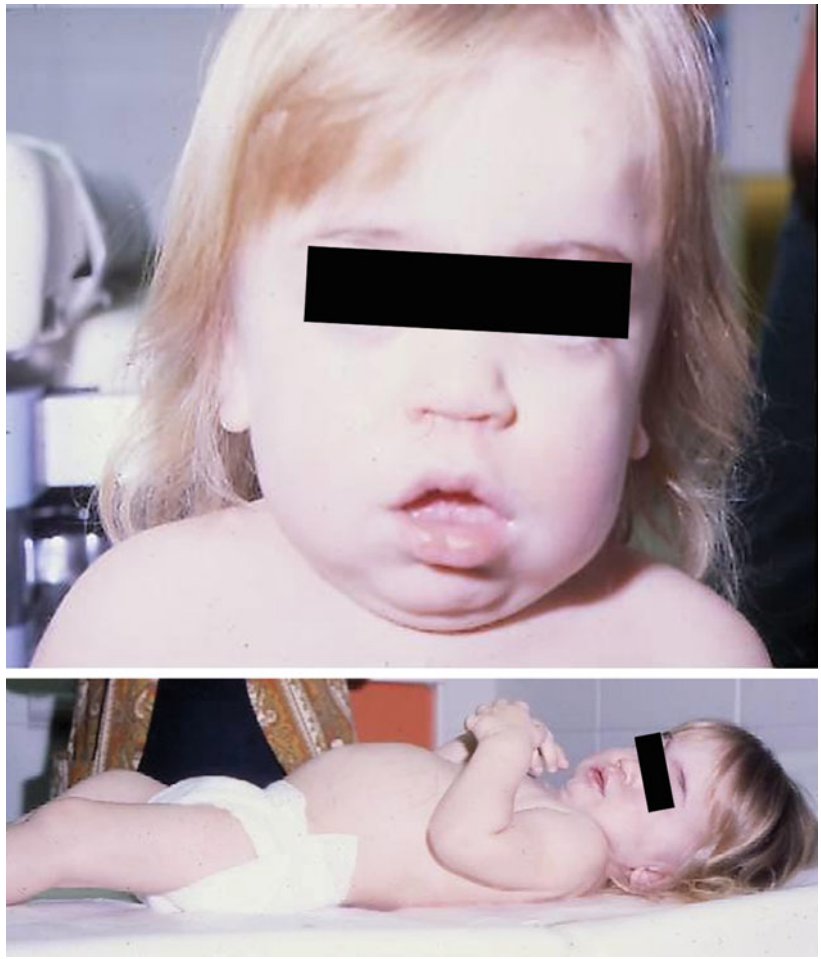

Fig. 1 (**a**, **b**) A child with Hurler syndrome showing a large head with frontal bossing, coarse facial features, ocular hypertelorism, cloudy (steamy) cornea, depressed nasal bridge, large tongue, short neck, protuberant abdomen, umbilical hernia, stiff joints, and claw hands

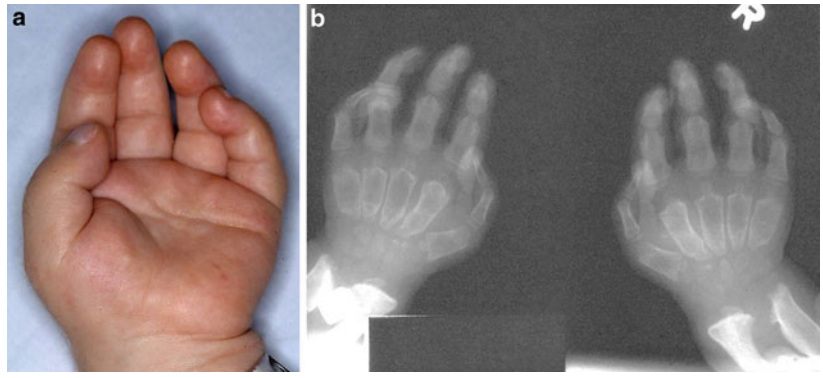

Fig. 2 (**a**, **b**) Claw hand. The radiographs show thick bullet-shaped phalanges, proximal narrowing of the metacarpals, poorly ossified carpal bones, and angulation toward each other of the distal ends of the radius and the ulnar

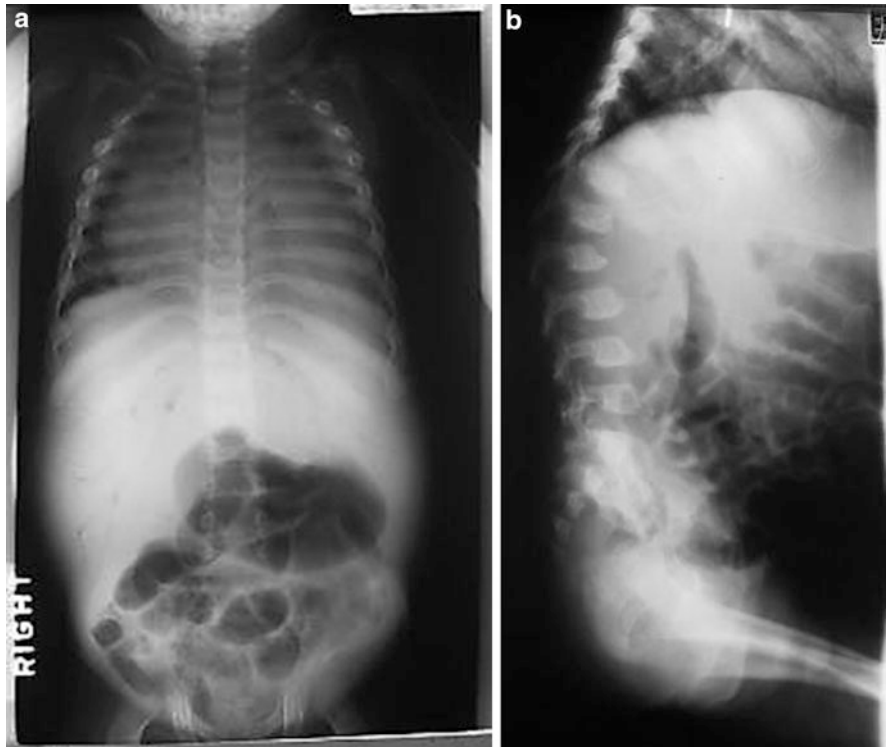

Fig. 3 (**a**, **b**) Radiographs showing oar-shaped ribs with relatively narrow proximal portion, narrow iliac bodies and flaring wings, shallow acetabula, coxa valga, anterior wedging of the lumbar vertebrae, decreased AP diameter of the vertebral bodies with posterior scalloping, and marked thoracolumbar gibbus

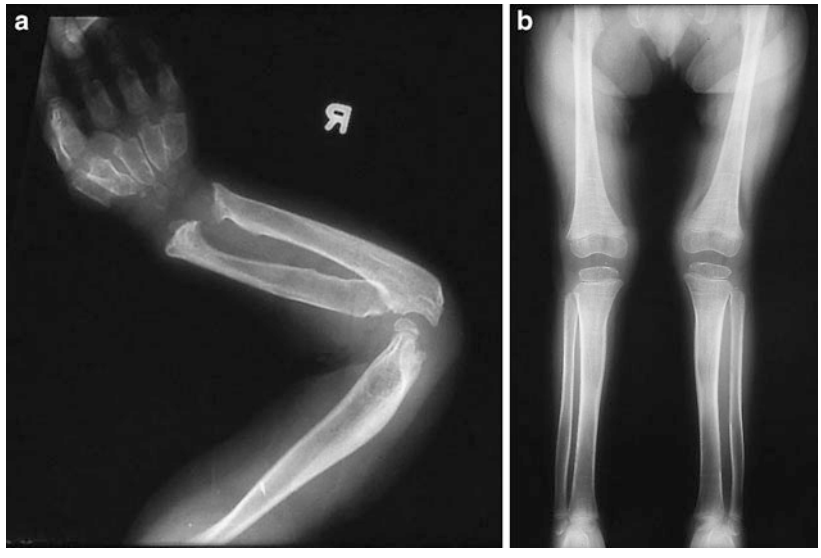

Fig. 4 (**a**, **b**) Radiograph of the upper extremities shows the lack of normal modeling and tabulation of the diaphyses, leading to short tubular bones. The radial and ulnar articular surfaces are angulated toward each other. Marked irregularity and retarded ossification of the carpal bones are noted. The findings in the lower extremities are less marked

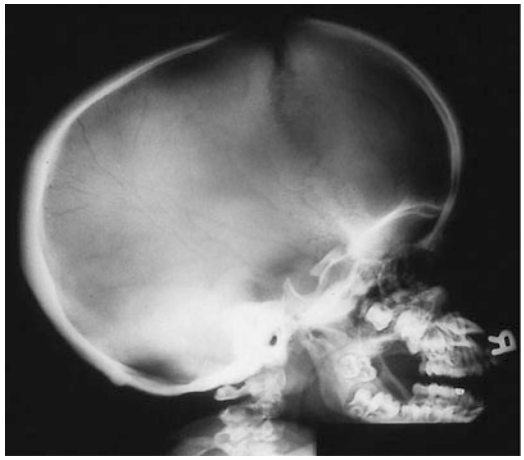

Fig. 5 Skull radiograph showing a large scaphocephalic calvarium with early appearance of the J-shaped sella turcica

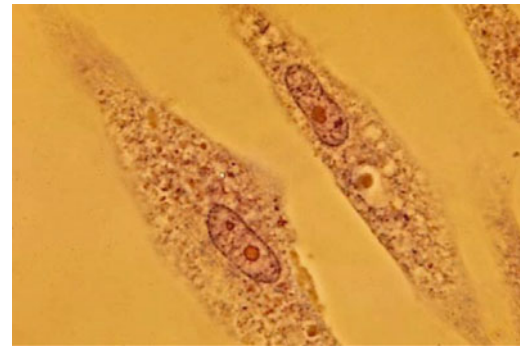

Fig. 7 Metachromasia of the cultured fibroblasts

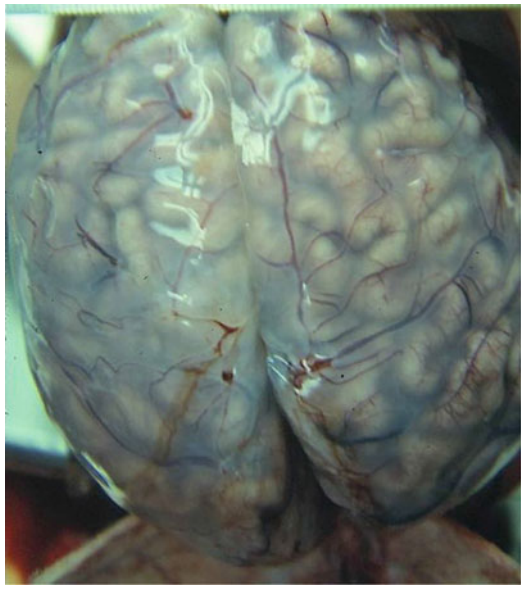

Fig. 6 Postmortem findings of the brain showing cloudy leptomeninges secondary to cloudy CSF

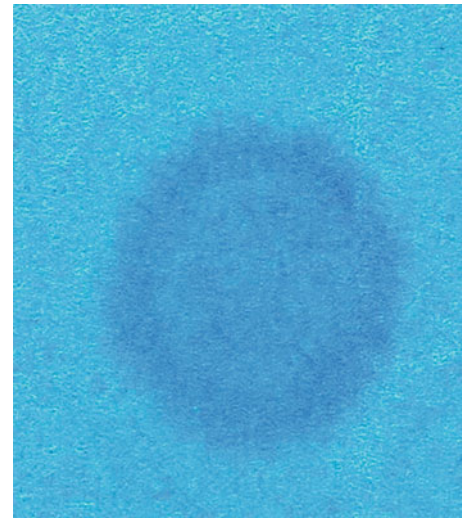

Fig. 8 Positive MPS spot test

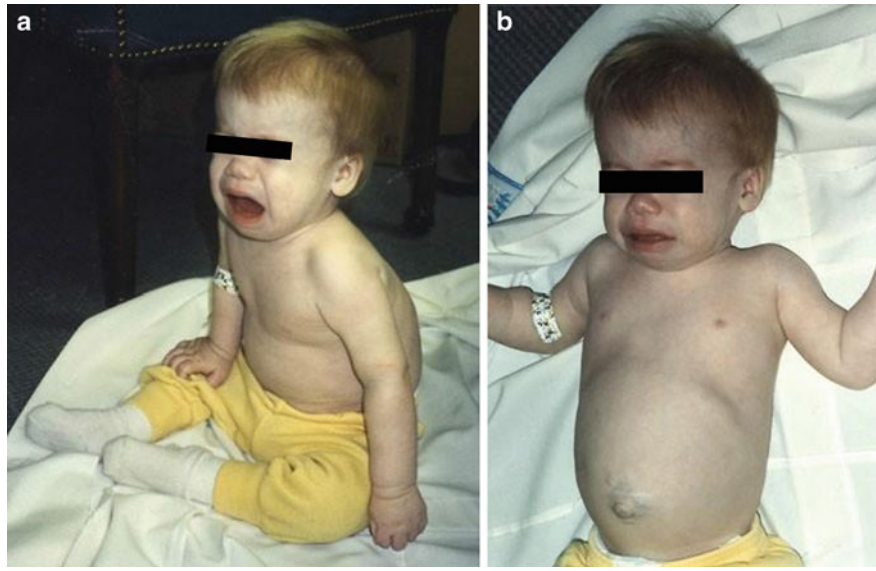

Fig. 9 (**a**, **b**) A 14-month-old boy with Hurler syndrome showing a large head, coarse facies, protuberant abdomen, umbilical hernia, a lumbar gibbus, and claw hands. The radiographs showed cardiomegaly, thickened ribs, and beaked vertebral body (L2). The α-L-iduronidase enzyme level was 0.0 (87.10–190.50 nmol/mg/h)

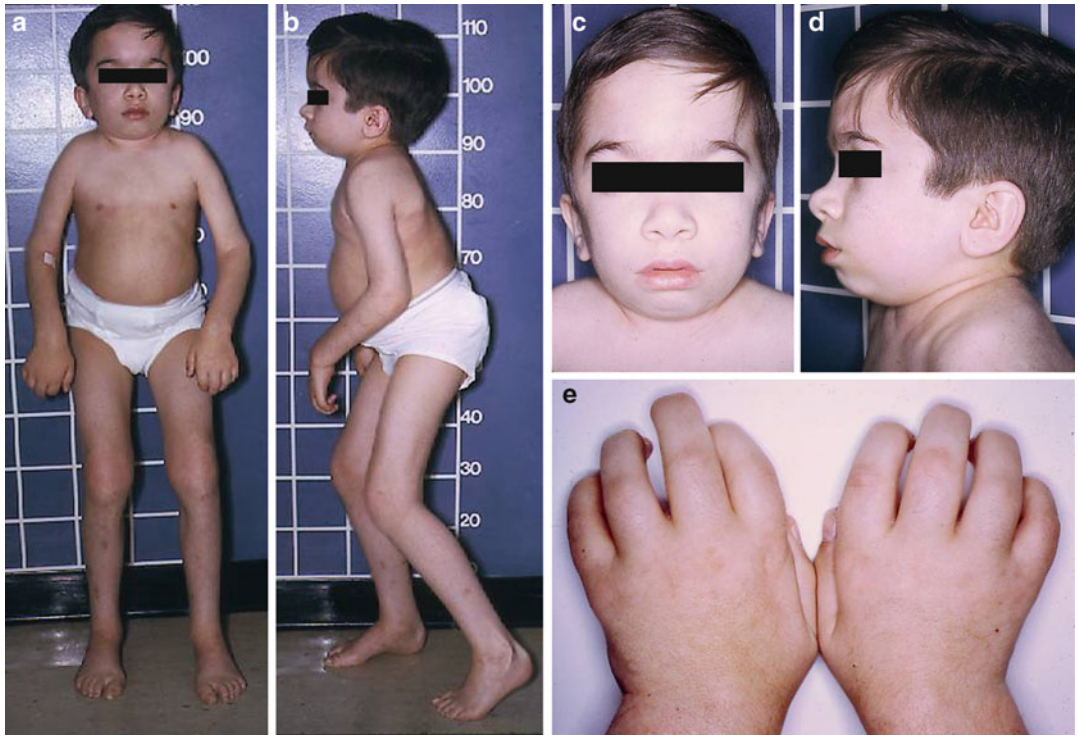

Fig. 10 A 14-year-old boy with Hurler–Scheie compound showing short stature, semi-crouching stance, joint stiffness (**a**, **b**), coarse facies (**c**, **d**), and claw hands (**e**). When he was 3½ years old, he started to complain difficulty in raising his arms above his head and difficulty in moving his hands and fingers because of bent fingers and joint contractures. He was noted to have dwarfism; coarse thickened skin; hirsutism; a big head with frontal bossing; coarse facies with hypertelorism; cloudy cornea; large lips and large tongue; short neck; short trunk with a mild kyphosis; hepatomegaly; claw hands; anteriorly converted shoulders; protuberant abdomen; flexion contractures of elbows, wrists, and knees; and crouching stance. The urine was positive for mucopolysaccharide, and the blood was positive for metachromasia. Skin fibroblasts were deficient in α-L-iduronidase

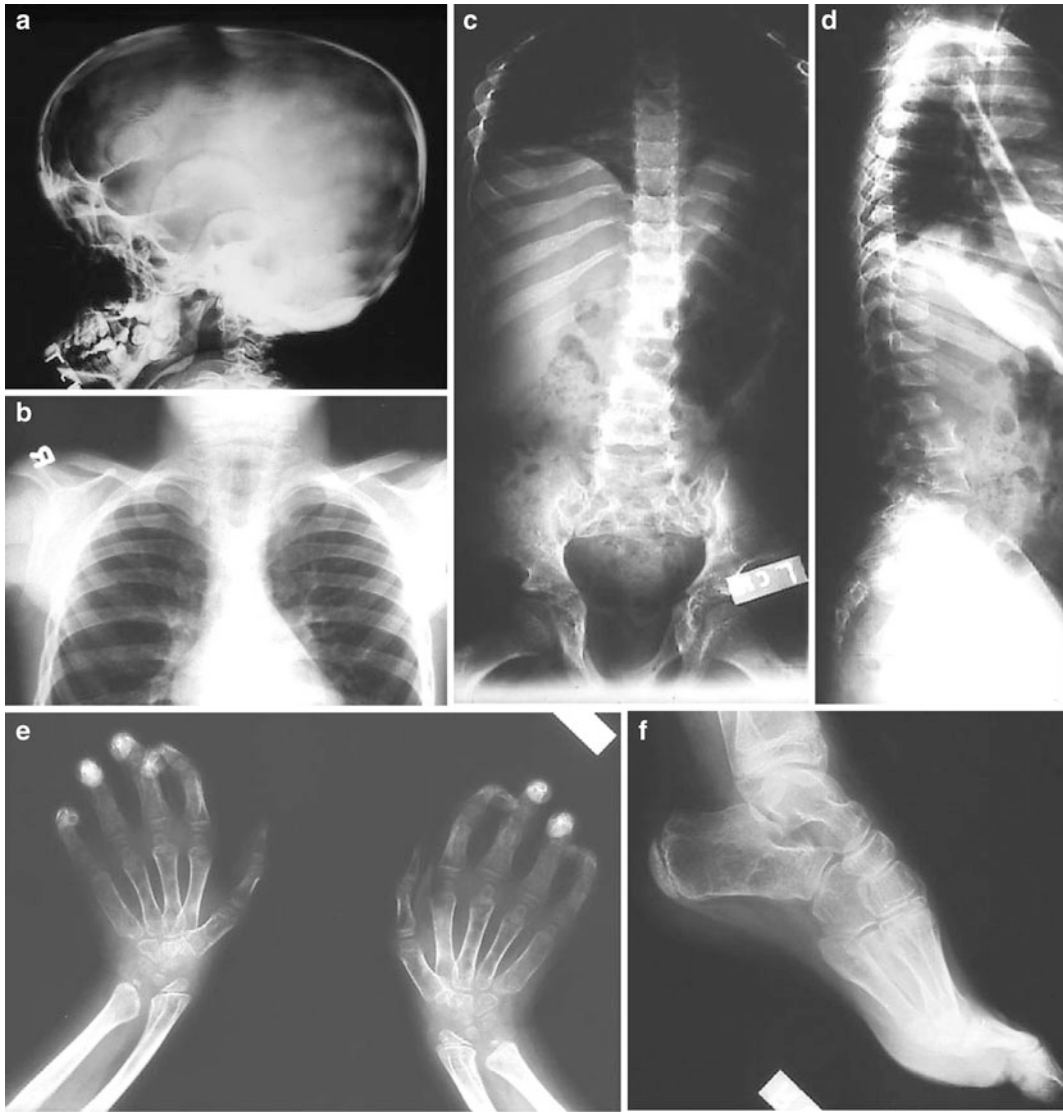

Fig. 11 Radiographs. The skull (**a**) shows macrocephaly, frontal bossing, small and airless mastoids, and anterior pocketing of the sella turcica ("shoe-shaped" or "J-shaped" sella). Clavicles (**b**) are short with widened medial aspects of both clavicles. Ribs are oar shaped and wide in their lateral and anterior portions with moderate narrowing of the paravertebral portions of the lower ribs (**c**, **d**). Vertebral bodies have concaved anterior and posterior margins and decreased in sagittal diameters. The second lumbar vertebra was hypoplastic with anterior inferior beaking forming almost a hook-shaped deformity. Claw hands were present with tapering of both distal ends of radius and ulna to form a "V shape" (**e**). Carpal bones were small, irregular, and crowded together. Metacarpals and phalanges were wide and short with proximal pointing of metacarpals. Bone age was retarded. Pes cavus was present (**f**)

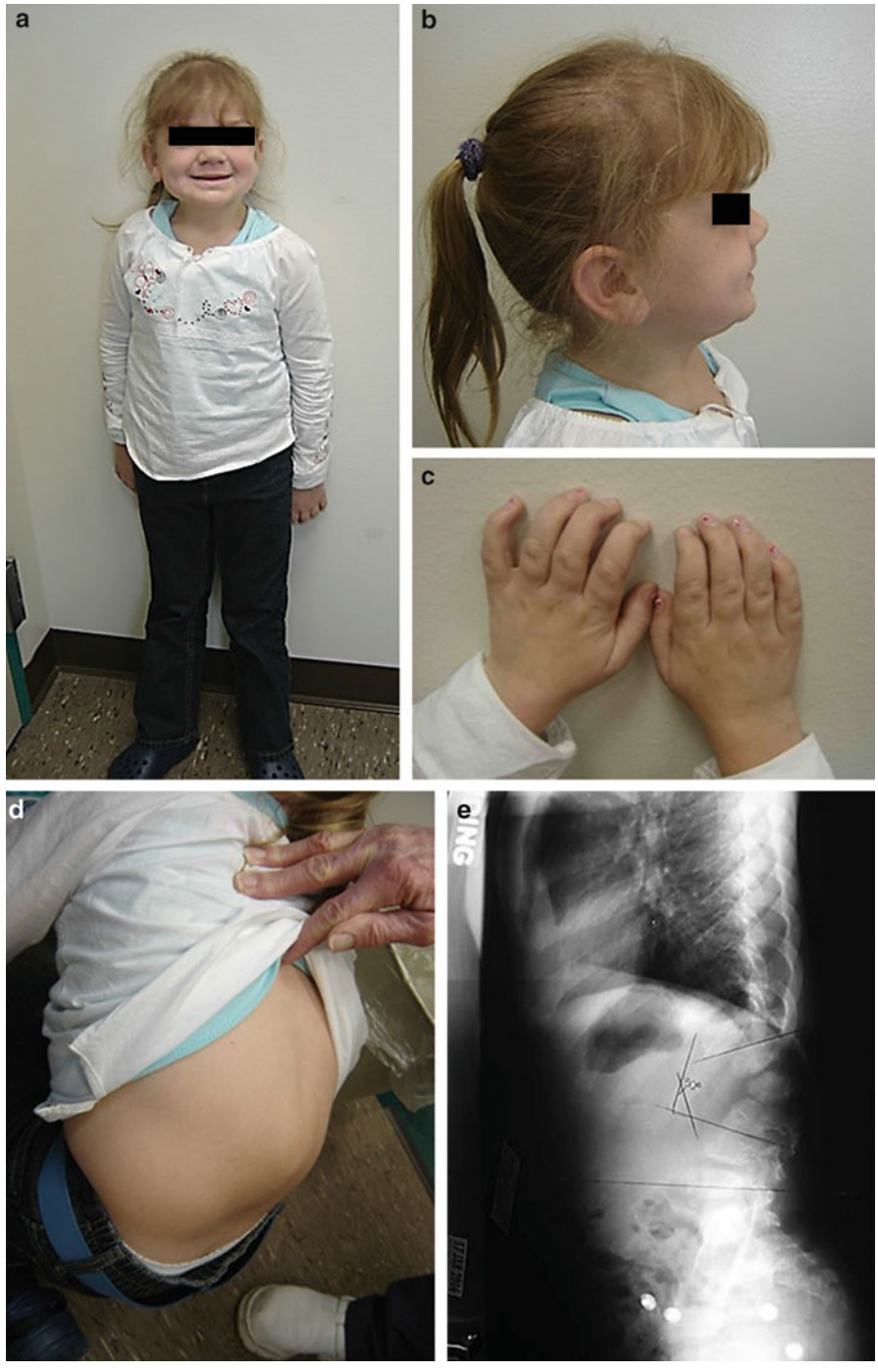

Fig. 12 (**a**–**e**) A 7-year-old girl was diagnosed to have Hurler syndrome at the age of 2. She received a male, 4/6 HLA-matched unrelated umbilical cord blood transplant. She engrafted quickly with an absolute neutrophil count greater than 500 on day +28. Her transplant complications included a *Klebsiella* UTI prior to admission, mucositis, medicine-induced hypertension controlled with nifedipine, diarrhea treated with Flagyl empirically, and graft-versus-host disease. Presently, she has less coarse facial features, resolving cloudy cornea, and improved cognitive capacity, but still has some claw hands and lumbar gibbus which are illustrated radiographically

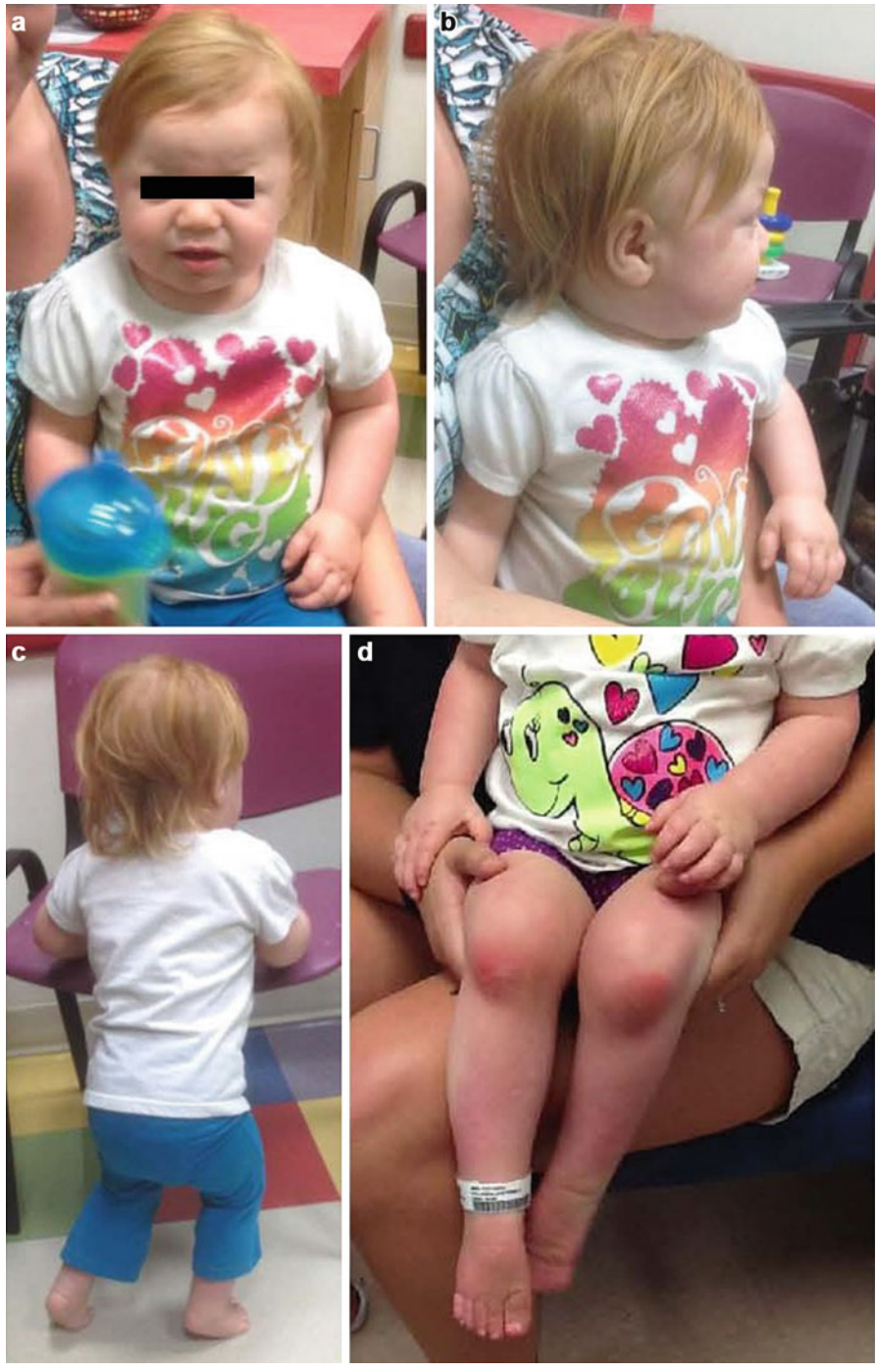

Fig. 13 (**a**–**d**) This is a 2 year-old girl evaluated originally for possible partial biotinidase deficiency from a newborn screening test. After a series of testings, she was found to be just a carrier for biotinidase deficiency (please see the chapter on "► Biotinidase Deficiency"). During the course of evaluation, she was noticed to have global delay, short stature, coarse facies, claw hands, and semi-crouching stance with knee crawling. The clinical and the following radiographic features (dysostosis multiplex) suggest Hurler syndrome. Urinary excretion of dermatan sulfate and heparin sulfate was elevated. Mucopolysaccharides were 171.9 which is markedly elevated (control:

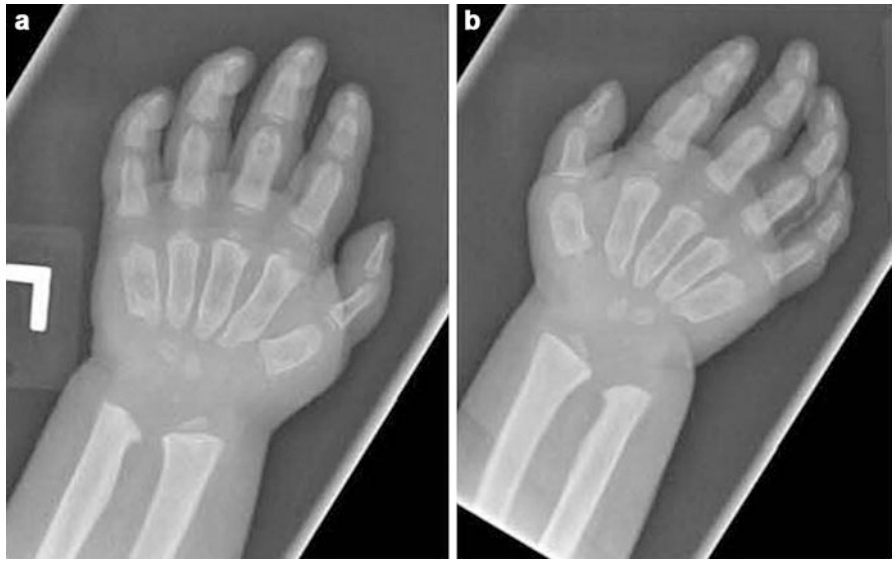

Fig. 14 (**a**, **b**) Radiographs of both hands showed claw hands, thickened bullet-shaped phalanges, proximal tapering of second to fifth metacarpals with widening of distal metacarpals, markedly retarded carpal bones, and slight tilting of distal radius and ulnar

Fig. 13 (continued) <24.0 mg/mmol). Lysosomal enzyme panel showed absent alpha-L-iduronidase activity which was consistent with the diagnosis of Hurler syndrome. IDUA gene sequencing showed homozygous in the IDUA gene for a sequence variant defined as c.1205G > A and predicted to result in premature termination p.Trp402Stop. This variant was documented as causative for MPS I. This result is consistent with diagnosis of MPS I. Interestingly, chromosome microarray analysis showed multiple regions of homozygosity >5 Mb including 4p16.3-p15.2 in which Hurler syndrome gene is located in 4p16.3

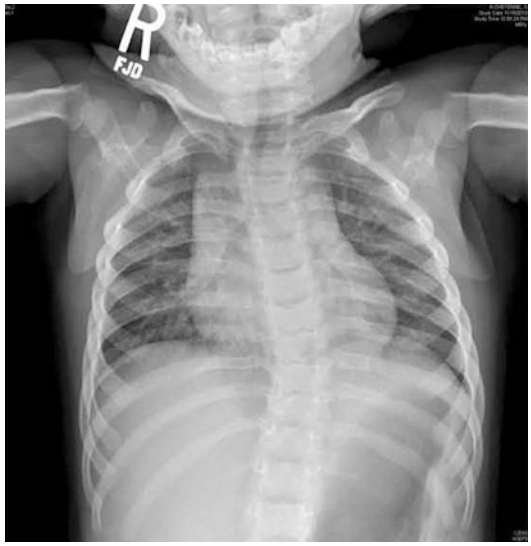

Fig. 15 AP view of the chest showed levoscoliotic curvature of lower thoracic spine, slight constriction of the posterior ribs at the costochondral joint junction (right, 9th to 11th; left, 11th), thickened scapula, and short and irregular clavicles

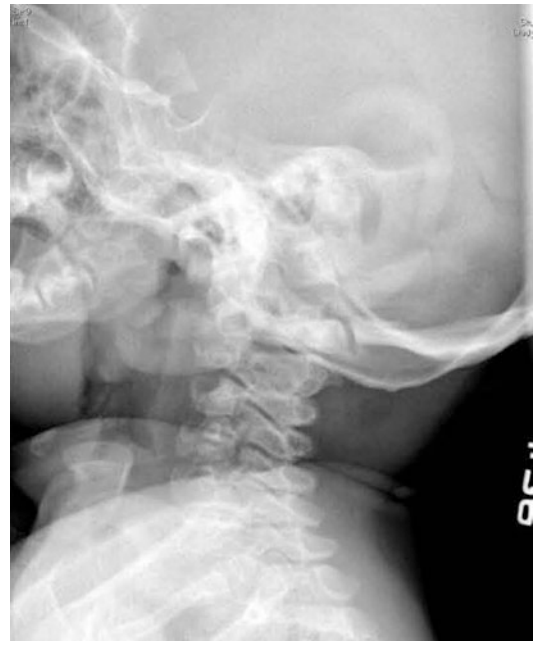

Fig. 17 Lateral view of the skull showed J-shaped sella turcica

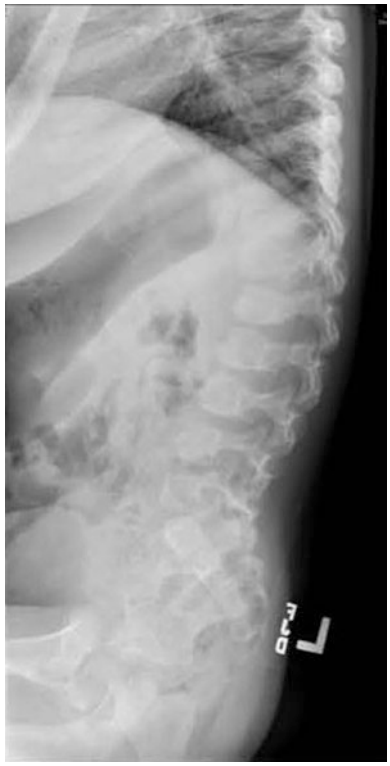

Fig. 16 Lateral lumbar spine showed anterior beaking of L1 and L2