Mucopolysaccharidosis 3

Contents

In 1962 and 1963, Sanfilippo et al. described eight children with mental retardation and heparan sulfate mucopolysaccharidoses and delineated the syndrome which now bears his name. Earlier in 1961, Harris reported a 6-year-old girl with hepatosplenomegaly, a normal skeletal survey, and excretion of large amounts of heparan sulfate in the urine. Sanfilippo syndrome is one of the most common mucopolysaccharidoses (MPS) (1/24,000–1/200,000).

Sanfilippo syndrome is comprised of four biochemically heterogeneous types (MPS IIIA, IIIB, IIIC, and IIID), which are clinically indistinguishable. Because the deficiency of these four various lysosomal enzymes involved the same breakdown of heparan sulfate, their clinical phenotype is similar. Type A is the most common type of MPS III in Northwest Europe, while type B is the most frequent type in Southeast Europe (Meikle et al. 1999; Poorthuis et al. 1999; Baehner et al. 2005). Types C and D appear to be much rarer (Valstar et al. 2008).

Synonyms and Related Disorders

Sanfilippo Syndrome

Genetics/Basic Defects

1. Inheritance: autosomal recessive.
2. Genetic heterogeneity (Van de Kamp et al. 1981).
3. Failure to degrade heparan sulfate may result from deficiency of one of the following four lysosomal enzymes (Bodamer et al. 2014):
   1. MPS IIIA caused by deficient heparan *N*-sulfatase (sulfamidase) (Karpova et al. 1996; Blanch et al. 1997; Bunge et al. 1997; Chabas et al. 2001)
   2. MPS IIIB caused by deficient α-*N*-acetylglucosaminidase (Beesley et al. 1998, 2005; Bunge et al. 1999)
   3. MPS IIIC caused by deficient acetyl-CoA:α-glucosaminide-*N*-acetyltransferase
   4. MPS IIID caused by deficient *N*-acetyl-α-glucosamine-6-sulfatase (Beesley et al. 2003)
4. Four subtypes of MPS III (Bodamer et al. 2014):
   1. Clinically indistinguishable
   2. Each characterized by deficiency of a different enzyme

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3. MPS IIIA mapped to 17q25.3
4. MPS IIIB mapped to 17q21
5. MPS IIIC mapped to 8p11.1
6. MPS IIID mapped to 12q14

Clinical Features

1. Severe CNS involvement (Nidiffer and Kelly 1983):
    1. Developmental milestones near normal prior to age 3–4 years.
    2. Developmental delay, especially in speech (first stage usually starts between 1 and 4 years of age).
    3. Behavioral problems (second stage usually starts around 3–4 years):
        1. Aggressiveness
        2. Hyperactivity
        3. Attention deficit
        4. Temper tantrums
        5. Destructive behavior
        6. Physical aggression
        7. Sleep disturbance:
            1. Setting difficulties
            2. Night walking
            3. Sometimes awake all night
            4. Crying out
            5. Wandering around the house
            6. Entering parents' bed
            7. Talking in sleep
            8. Body rocking
            9. Chewing bedclothes
        8. Poor attention span
        9. Marked mood swings
        10. Self-injury
    4. Progressive motor difficulties due to spasticity and joint stiffness and slowly disappearing behavioral problems, starting about 10 years of age (marking the third and final stage).
    5. Severe hearing loss common in the moderate to severely affected patient.
    6. Severe neurologic degeneration occurring in most patients by 6–10 years of age, accompanied by rapid deterioration of social and adaptive skills (mental deterioration).
    7. Progressive dementia resulting in withdrawal and losing contact with the environment.
    8. Seizures: uncommon.
    9. Patients usually die at the end of the second or beginning of the third decade of life, although survival into the fourth decade has been reported.
2. Mild somatic disease:
    1. Coarse hair (hirsutism): hypertrichosis often present, especially on the back
    2. Macrocephaly
    3. Copious nasal discharge
    4. Repeated upper respiratory tract infections
    5. Cardiac signs and symptoms much lesser degree compared to other types of mucopolysaccharidosis
    6. Mild hepatosplenomegaly
    7. Joint stiffness
    8. Recurrent and sometimes severe diarrhea, usually improves in later childhood
    9. Early onset of puberty
3. Prognosis:
    1. Type A:
        1. The most severe type
        2. Earlier onset
        3. More rapid progression of symptoms (natural history) (Buhrman et al. 2014):
            1. Severe hearing loss and speech delay, followed by a rapid decline in cognitive skills by 3 years of age.
            2. Significant somatic disease occurs in more than half of the patients.
            3. Behavioral difficulties presented between 2 and 4 years of age during a rapid period of cognitive decline.
            4. Gross motor abilities are maintained during this period, which results in an active child with impaired cognition.
            5. Sleep difficulties are concurrent with the period of cognitive degeneration.
        4. Shorter survival: death usually by late teens
    2. Type B: known to remain functional into the third or even fourth decades
    3. Type C: clinically heterogeneous

4. Type D (Jones et al. 1997):
    1. Least common type
    2. Clinically heterogeneous

Diagnostic Investigations

1. Increased urinary excretion of heparan sulfate.
2. Quantitative urinary glycosaminoglycan analysis (Bodamer et al. 2014) is strongly recommended, and measurement of disaccharides, heparin cofactor II–thrombin complex, and gangliosides is also used (Andrade et al. 2015).
3. Growth charts for height and weight for males and females are available for MPS III (de Ruijter et al. 2014).
4. Imaging features:
    1. Radiography: mild degree of dysostosis multiplex
    2. Echocardiography for rare cardiac abnormalities
    3. CT:
        1. Mild to moderate cortical atrophy at onset
        2. Severe cortical atrophy at late stage
    4. MRI (Barone et al. 1999):
        1. Cortical atrophy.
        2. Corpus callosum atrophy.
        3. Abnormal or delayed myelination.
        4. MRI findings may precede the onset of overt neurological symptoms.
5. Biochemical analysis (Defendi and Varma 2009):
    1. Biochemical differentiation of the different forms within MPS II is possible, and diagnosis is confirmed by specific enzymatic assay:
        1. Deficient heparan *N*-sulfatase (type A)
        2. Deficient *N*-acetylglucosaminidase (type B)
        3. Deficient α-glucosamine-*N*-acetyltransferase (type C)
        4. Deficient *N*-acetyl-α-glucosamine-6-sulfatase (type D)
    2. Enzymatic activity for all types of MPS III may be assayed in cultured skin fibroblasts and in peripheral blood leukocytes.
    3. Enzyme activity of the different enzymes in blood serum, leukocytes, or fibroblasts and mutational analysis for *SGSH*, *NAGLU*, *HGSNAT*, or *GNS* genes are required to confirm diagnosis and differentiate four subtypes of MPS III (Andrade et al. 2015).
6. Mutation studies are available clinically by sequence analysis and deletion/duplication analysis:
    1. MPS IIIA (Beesley et al. 2000; Yogalingam and Hopwood 2001; Lee-Chen et al. 2002a; Di Natale et al. 2003):
        1. Missense mutations (most common)
        2. Premature termination mutations
        3. Small deletion mutations
    2. MPS IIIB (Zhao et al. 1996; Yogalingam and Hopwood 2001; Lee-Chen et al. 2002b):
        1. Great molecular heterogeneity
        2. Most mutations: private mutations
    3. MPS IIIC: no mutation analysis available currently
    4. MPS IIID: frameshift and premature termination mutation
7. Very recent breakthroughs in high-throughput methods for sequencing only the protein-coding regions of the genome, called whole exome sequencing or targeted exome capture, present tempting future screening and diagnostic possibilities (Bodamer et al. 2014).
8. Carrier detection (Vance et al. 1981; Toone and Applegarth 1988).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sib: 25%
    2. Patient's offspring: not reproducing due to mental retardation
2. Prenatal diagnosis (Di Natale et al. 1999):
    1. Fetuses at risk for MPS IIIA:
        1. Measuring sulfamidase activity using radioactive assay in CVS and amniocytes (Thompson et al. 1993)

2. Using fluorimetric sulfamidase assay in CVS and amniocytes (Kleijer et al. 1996)
3. Molecular diagnosis in characterized families

2. Fetuses at risk for MPS IIIB:
   1. Assay of α-*N*-acetylglucosaminidase activity in cultured amniocytes (Mossman et al. 1983) and CVS (Kleijer et al. 1984; Minelli et al. 1988)
   2. Increased level of heparan sulfate in amniotic fluid by two-dimensional electrophoresis of glycosaminoglycans: used as an adjunctive method in prenatal diagnosis
   3. Molecular diagnosis in characterized families
3. Fetuses at risk for MPS IIIC:
   1. Assay of acetyl-CoA:α-glucosamine-*N*-acetyltransferase in amniocytes (Maire et al. 1993) and CVS (di Natale et al. 1987; He et al. 1994)
   2. Molecular diagnosis in characterized families
4. Fetuses at risk for MPS IIID:
   1. Spectrophotometric assay for the *N*-acetyl-α-glucosamine-6-sulfatase activity (Nowakowski et al. 1989)
   2. Molecular diagnosis in characterized families
5. Diagnostics using free fetal DNA or fetal cells recovered from maternal circulation to directly detect mutations causing the MPS III phenotype will enable prenatal diagnosis of MPS III without the need of invasive sampling procedures (Dhallan et al. 2004).

3. Preimplantation genetic diagnosis (Hopwood 2005):
   1. Allows embryos to be tested for MPS III before they enter the uterus and pregnancy begins.
   2. This requires embryos, obtained by in vitro fertilization, to undergo a biopsy procedure in which one or two cells are removed and tested for the specific disorder.
   3. Only embryos shown to be free of MPS III are then implanted (Thornhill and Snow 2002).

4. Management (Cleary and Wraith 1993):
   1. Supportive treatments:
      1. Antibiotics for otitis media and respiratory tract infections
      2. Anticonvulsants for seizure activities
   2. Muscle relaxants for painful spasms.
   3. Gastrostomy to maintain adequate nutrition.
   4. Special education program.
   5. Behavioral management to allow the family to function as near normal as possible:
      1. Alteration to the physical environment within home
      2. Drug treatment to control hyperactivity and aggression
   6. Physical therapy to maintain joint mobility.
   7. Recommend monitoring bone mineral density by dual-energy X-ray absorptiometry and checking vitamin D metabolism to assess low bone mass and fracture risk in older MPS III patients with immobility (Nur et al. 2016).
   8. Wheelchair for transportation.
   9. Respite care: availability of suitable respite accommodation.
   10. Identify professional and community resources.
   11. Risperidone treatment of behavioral disorder in children with MPS IIIA: appeared to be safe and effective (Ucar et al. 2010).
   12. Bone marrow transplantation (Vellodi et al. 1992; Sivakumur and Wraith 1999):
      1. Biochemical correction readily achievable
      2. Disappointing intellectual outcome
   13. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective (Aldenhoven et al. 2015).

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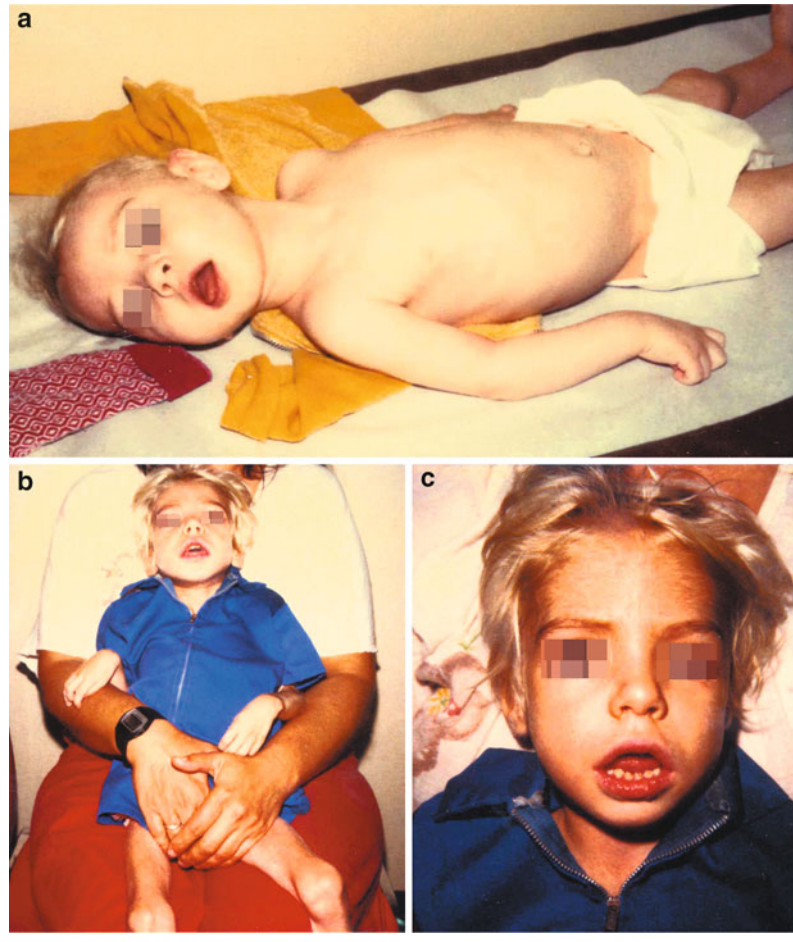

Fig. 1 (**a**–**c**) A child with MPS IIIA at 8 months (**a**) and 3 years (**b**, **c**)

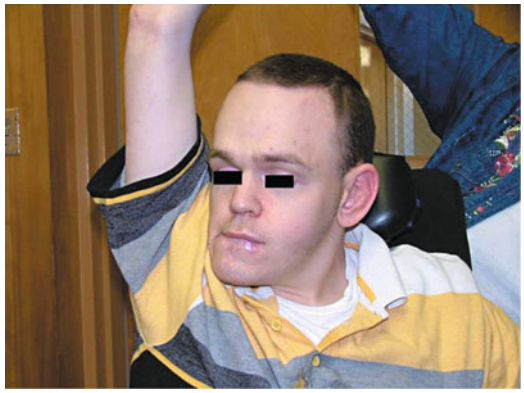

Fig. 2 A 32-year-old male with Sanfilippo syndrome type A showing mental retardation and severe behavioral problems. Molecular genetic analysis revealed heparan sulfamidase (SGSH) gene mutations. A C > T substitution was detected at nucleotide 892 resulting in a serine being replaced by a proline at amino acid 298 (S298P). The second nucleotide change resulted in insertion of a cystine at nucleotide 1,028 which creates a frameshift and premature truncation of protein (1028insC). The detection of two mutations in the heparan sulfamidase gene is associated with Sanfilippo A syndrome

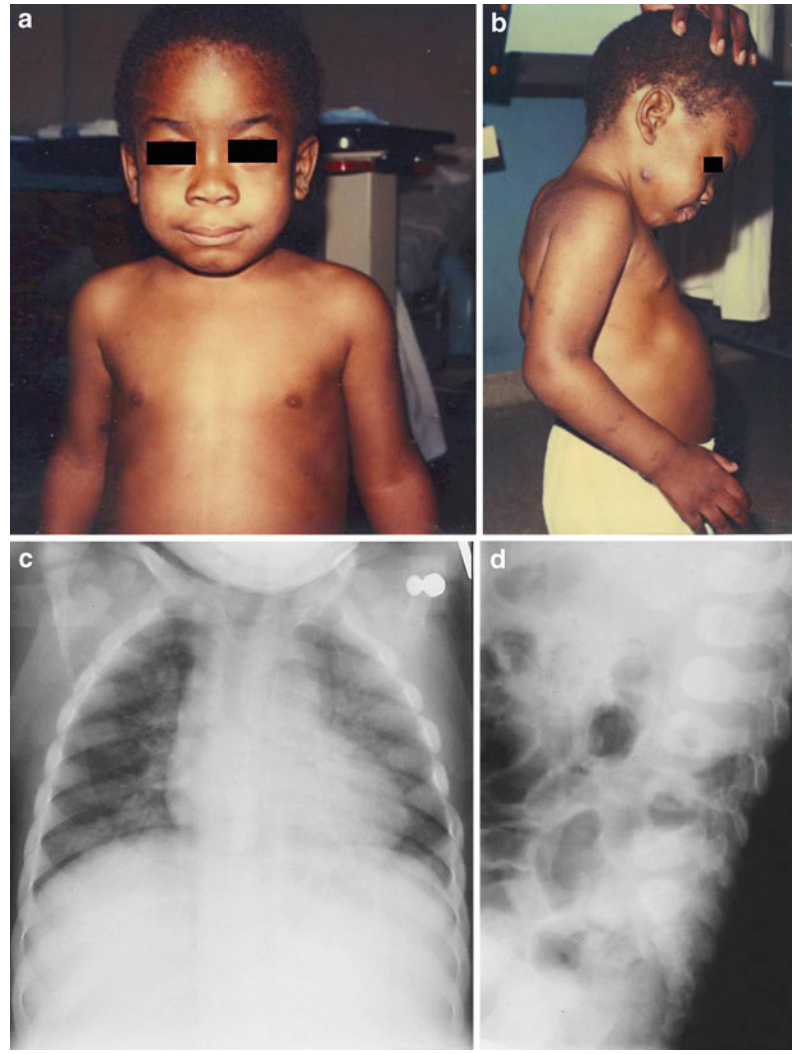

Fig. 3 (**a**–**d**) A child with MPS IIIB at 3 years of age (**a**, **b**). The radiographs (**c**, **d**) show mild degree of dysostosis multiplex