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Scoring Evaluation of the Natural Course of Mucopolysaccharidosis Type IIIA (Sanfilippo Syndrome Type A)

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ABSTRACT

OBJECTIVE. Mucopolysaccharidosis types IIIA through IIID (Sanfilippo syndrome) are caused by deficiencies of enzymes involved in the degradation of heparan sulfate. The onset and severity of the disease are highly variable. The purpose of this study was to describe the natural course of mucopolysaccharidosis type IIIA in a large cohort of patients.

PATIENTS AND METHODS. The natural course of mucopolysaccharidosis type IIIA was assessed in 71 patients by using a detailed questionnaire and a 4-point scoring system and compared with the course of the disease in 14 patients with mucopolysaccharidosis type IIIB and 4 patients with mucopolysaccharidosis type IIIC.

RESULTS. In the cohort of patients with mucopolysaccharidosis type IIIA, first symptoms of disease were observed, on average, at 7 months of age. Speech and motor development were delayed in 66.2% and 33.9% of patients, respectively. The median age at diagnosis was 4.5 years. The onset of regression in speech, motor, and cognitive function was observed at an average age of 3.3 years. The loss of all 3 of the assessed abilities was observed at an average age of 12.5 years. Speech was lost before motor and cognitive functions. In a small group of patients who were >12.5 years of age (9.9%), speech, motor, and cognitive skills were partially preserved up to a maximum age of 23.8 years.

CONCLUSIONS. To our knowledge, this is the first systematic and comprehensive study on the natural course of mucopolysaccharidosis type IIIA. The 4-point scoring system may be used to classify patients into groups with a rapid or slower course of the disease. This may have an important impact on parental counseling as well as therapeutic interventions.

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Key Words

mucopolysaccharidosis type III, Sanfilippo syndrome, natural course, scoring system

Abbreviations

MPS—mucopolysaccharidosis
FPSS—4-point scoring system
TDS—total disability score

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MUCOPOLYSACCHARIDOSIS (MPS) TYPE III (Sanfilippo syndrome) is a genetically and clinically heterogeneous group of diseases caused by the deficiency of 1 of 4 enzymes (defining subtypes A–D) involved in the degradation of heparan sulfate. The absence of 1 of these enzymes leads to the accumulation and urinary secretion of heparan sulfate. MPS IIIA arises when *N*-sulfo-glucosamine sulfohydrolase activity (sulfamidase, EC 3.10.1.1) is lost. MPS IIIB and C are caused by defective α -*N*-acetylglucosaminidase (EC 3.2.1.50) and heparan- α -glucosaminide *N*-acetyltransferase (EC 2.1.3.78), respectively. The activity of *N*-acetylglucosamine-6-sulfatase (EC 3.1.6.14) is deficient in patients with MPS IIID. All of the MPS III subtypes are inherited in an autosomal recessive manner.¹ The incidence of MPS III in Germany has been estimated as 1 in 63 700 births.² MPS IIIA is the most common subtype in Northern Europe, whereas MPS IIIB is more prevalent in Southern Europe.^{3,4}

The clinical features of the different enzyme deficiencies are difficult to distinguish. Patients with MPS III have been reported to be normal at birth and develop normally during the first year of life. Developmental delay becomes apparent in early childhood, and children may exhibit behavioral abnormalities, sleep disturbances, and speech delay. Somatic features are often mild and variable. Patients may show coarse facial features, mild skeletal dysostosis multiplex, and hepatosplenomegaly. Mental retardation becomes obvious over time, and progressive neurologic degeneration occurs. Patients generally die within the second decade of life; however, survival into the third or fourth decade has also been reported.⁵ There may be differences in the severity of disease in the different subtypes. Whereas adult onset of dementia has been reported in MPS IIIB patients,^{6,7} dementia is apparent in the majority of patients with MPS IIIA by the age of 6 years.⁸ Progression of the disease is thought to be more rapid in MPS IIIA than in MPS IIIB and C. However, the clinical phenotype of patients with the same subtype of MPS III, even in siblings, is highly variable.^{9–13} The severity of MPS IIIC is reported to lie between that of MPS IIIA and B.¹⁴ MPS IIID is very rare and also heterogeneous.^{15,16} The variability in the clinical phenotype of patients with MPS III is presumed to be because of variations in residual enzyme activity, caused by the different homozygous and compound heterozygous mutations.^{3,17–19}

In this study, the natural course of MPS IIIA was investigated in a group of 71 patients and compared, where possible, with the progression of the disease in 14 patients with MPS IIIB and 4 patients with MPS IIIC. The study was based on a questionnaire and a 4-point scoring system (FPSS). This study describes the natural course of the disease in a large cohort of German patients with MPS III.

PATIENTS AND METHODS

Patients

To obtain a representative cohort of patients, families were asked to participate in the study by an information sheet sent out through the German MPS Society. Patients were also recruited from the MPS outpatient clinic of the University Medical Center in Hamburg-Eppendorf, as well as being referred by colleagues. From 170 information sheets sent out, 97 patients' families (57.1%) agreed to participate in the study. Interviews with the parents and/or grandparents of patients were conducted between August 2005 and March 2006. The families were asked to provide material on the diagnosis and clinical course of the disease (medical reports, kindergarten/school reports, photographs at different ages, etc) and to give consent that additional reports from diagnostic laboratories, genetic departments, general pediatricians, and metabolic centers be gathered. Two families did not provide all of the material required and were excluded from the study. Five families left the study for personal reasons (eg, recent death of the child). Classification of the MPS III subtype was made through the analysis of enzyme activities and the molecular gene defect. One patient had an unclassified MPS III subtype and, therefore, was excluded. In total, 89 patients with MPS III, classified into subtypes, took part in the study. The relative distribution of the different subtypes in the study population was similar to that found in German patients with MPS by Baehner et al.² In addition, the 71 patients in the MPS IIIA cohort seem to be representative of the general MPS IIIA population, based on analysis of the range of mutations found in the sulfamidase gene of the study population (unpublished data, 2007).

Questionnaire and Scoring System

Families were interviewed by using a detailed questionnaire that covered almost all aspects of the disease and an FPSS that assessed the degree of developmental regression over time. The questionnaire was completed using information provided by the patient's family members, doctors, teachers, and therapists. It contained 11 categories including the following: personal data, family history (consanguinity, ethnic origin, partnership, and siblings), pregnancy and delivery, diagnostic parameters (first symptoms, diagnosing medical center, enzyme activities, glycosaminoglycan excretion in urine, and mutation analysis), symptoms (dysmorphic facial features, vision and hearing impairment, heart and airway disease, inner organ enlargement, skeletal and joint disease, impairment of motor function, developmental delay, behavioral problems, sleep disturbances, neurologic symptoms, epilepsy, and diarrhea), and physical development/puberty (weight, growth and head circumference changes, pubarche, thelarche, and menarche). Data were also collected on therapies and medications, med-

ical and social care, kindergarten and school attendance, interests and hobbies, developmental regression, and death. The progression of the disease was tracked using a modified scoring system described previously for other neurodegenerative disorders of childhood.^{20,21} The FPSS assessed motor function, speech abilities, and cognitive function, retrospectively, over the course of disease in 3- to 6-month intervals. Scoring assessments were made as follows: 3 points for normal function, 2 points at the beginning of regression, 1 point where regression had progressed to a severe level, and 0 points where function was lost. Detailed information on the scoring method used in this study is given in Table 1. The total disability score (TDS) is the average of the motor function, speech, and cognitive function scores. The interviews and scoring assessments were all conducted by the same interviewer. The detailed questionnaire is available on request from the authors. The study was approved by the medical ethics committee of the Ärztekammer Hamburg.

MPS III Subtype Classification

MPS III subtype was determined through sulfamidase, α -N-acetylglucosaminidase, and heparan- α -glucosaminidase N-acetyltransferase activity analysis in either white blood cells or fibroblasts. Quantitative glycosaminoglycan analysis was performed using the dimethylmethylene blue method.²² Two-dimensional electrophoresis of urinary glycosaminoglycans was conducted as described previously.²³

Data Handling and Analysis

To protect patient privacy, each patient received a study number, which was used in all of the analyses. Personal data were separated from the questionnaire. All of the analyses were performed by using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL).

TABLE 1 FPSS for MPS Type III

Function	Performance	Score
Motor function ^a	Normal walking	3
	Clumsy walking	2
	Aided walking	1
	Wheel chair/immobile	0
Speech abilities ^a	Normal speech	3
	Impairment of speech	2
	Speech difficult to understand	1
Cognitive function	Loss of speech	0
	Normal cognitive function	3
	Deterioration of cognitive function	2
	Loss of interest in environment	1
	Unresponsiveness	0

^a In some patients, motor and speech development were never normal. In these case subjects, the scoring started at a score of 2.

RESULTS

A total of 89 patients with MPS III (51.7% males and 48.3% females) from 82 families were included in the study; this total was composed of 71 patients (79.8%) with subtype A, 14 patients (15.7%) with subtype B, and 4 patients (4.5%) with subtype C. No patients with MPS III D took part in the study. Ten patients (11.2%) had died at the time of data collection. The age and gender distribution of the study population at the time of data collection is shown in Table 2. Because of the low number of patients with subtypes B ($n = 14$) and C ($n = 4$), comparative statistical analysis of the data was not possible. Similarities in the clinical features, course, and progression of the disease, however, were mentioned, where relevant. The average age of patients with MPS IIIA at the time of data collection was 13.2 years (SD: 6.8 years [range: 1.8–32.8 years]).

Pregnancy, Delivery, and Early Developmental Milestones

Pregnancies were normal in the births of 80.3% of the children with MPS IIIA (57.1% MPS IIIB). Complications reported during pregnancy were cervix insufficiency (6.2%), infections (5.6%), and vaginal bleedings (4.2%). Previous miscarriages were observed in 29.2% of women (19 of 65). Six patients with MPS IIIA (8.5%) were born prematurely, which is within the range found in the general population.²⁴ Normal early developmental milestones were reached by 26.1% of the studied patients with MPS IIIA (14.3% type B). Normal speech development was defined as talking before 15 months and normal motor development as walking independently before 18 months.^{25,26} In 66.7% of the patients with MPS IIIA studied, speech development was delayed (71.4% type B). Two patients with MPS IIIA (7.3 and 8.5 years of age) had never spoken at the time of data collection. Motor development was delayed in 33.3% of the patients with MPS IIIA (50% type B). In 2 patients, parents could remember neither speech nor motor development milestones (excluded from evaluation). A delay of both speech and motor development was observed in 26.1% of the patients with MPS IIIA (35.7% type B). Data on the early development of the patients with MPS IIIA are summarized in Table 3.

First Symptoms and Diagnosis

First symptoms in patients with MPS IIIA were observed, on average, at 7 months of age (SD: 1.2 months [range: 0.0–4.5 months]). Although 67.6% of the patients with MPS IIIA first presented symptoms within the first year of life, the average age at diagnosis was 4.5 years (SD: 2.6 years [range: 0.25–13.8 years]). One third of the patients with MPS IIIA were diagnosed after 5 years of age. The relative distribution of the patients with MPS IIIB diagnosed at different ages was almost identical to the patients with MPS IIIA. Sleep disturbances and behavioral

TABLE 2 Age and Gender Distribution of the Studied MPS III Population

MPS III Subtype	Age (N = 89), n (Male/Female)							Total n (%)
	0–5 y	>5–10 y	>10–15 y	>15–20 y	>20–30 y	>30 y	Deceased	
A	4 (1/3)	19 (9/10)	20 (12/8)	10 (4/6)	8 (3/5)	2 (0/2)	8 (6/2)	71 (79.8)
B	2 (1/1)	3 (3/0)	2 (1/1)	2 (0/2)	2 (2/0)	1 (0/1)	2 (1/1)	14 (15.7)
C	0	1 (1/0)	2 (1/1)	0	1 (1/0)	0	0	4 (4.5)
Total	6 (2/4)	23 (13/10)	24 (14/10)	12 (4/8)	11 (6/5)	3 (0/3)	10 (7/3)	89 (100.0)

Data are for the time of data collection.

abnormalities (hyperactivity, aggressive behavior, and unawareness of dangerous situations) were both reported as being the first noticeable symptoms of the disease in 38% of the patients with MPS IIIA. One fifth of the patients with MPS IIIA first presented with speech delay (Table 4).

Clinical Presentation

Sixty-one patients (85.9%) showed coarse facial features. Ten patients at an age between 6.8 and 32.8 years did not show coarse facial features. Macrocephaly was present in 52 patients (73.2%) and microcephaly in 1 patient (1.4%), whereas 18 patients (25.4%) had a normal head circumference. Hearing impairment was reported in 32 patients (45.1%), and hearing aids were used by 21 of these patients. Eye testing was conducted in 39 (55.0%) of the patients with MPS IIIA. Refraction abnormalities were found in 14 patients (35.9%), myopia was apparent in 11 patients (28.2%), and hyperopia was found in 3 patients (7.7%). Strabismus was found in 2 patients (5.1%). No patients presented with corneal clouding. Heart disease, mainly mitral valve followed by aortic valve defects, was detected in 18 patients (25.4%) at the time of data collection. More than one third (38.0%) of the patients with MPS IIIA were never tested for heart disease. Organ enlargement was observed in 64 patients (90.1%). Hernia occurred in 54.9% of the patients with MPS IIIA. Hyperactivity occurred, on average, at 3.3 years of age (SD: 2.6 years [range: 0–17 years]) and declined at 8.8 years (SD: 2.6 years [range: 4.8–16 years]). Persistent nocturnal enuresis was observed in 74.6%, and persistent diurnal, as well as nocturnal enuresis, was reported in 64.8% of the patients with MPS IIIA. In 37 (52.1%) of the patients with MPS IIIA, seizures were reported at the time of data collection. In 68.1% of patients >10 years

TABLE 3 Early Developmental Milestones of Patients With MPS IIIA (N = 69)

Status	n (%)
Normal early development	18 (26.1)
Late talking (≥ 15 mo)	28 (40.6) ^a
Late walking (≥ 18 mo)	5 (7.2)
Late talking and walking	18 (26.1)

^aTwo patients never spoke.

of age, epilepsy was found (>15 years: 73.9%; >20 years: 81.8%). Epilepsy first presented, on average, at 10.9 years (SD: 4.4 years [range: 3.0–22.75 years]). Of the 71 patients with MPS IIIA studied, 69 (97.2%) showed mental retardation at the time of data collection.

Scoring of the Clinical Course

The clinical course of the disease was tracked using the FPSS, which assessed motor function, speech, and cognitive function (Table 1). The median scores for motor function, speech abilities, and cognitive function of all of the patients with MPS IIIA, by age, are shown in Fig 1. The onset of speech regression (score of 2) in patients with MPS IIIA was first observed at 2.8 years of age (SD: 1.9), whereas motor and cognitive functions began to regress at age 4.1 years (SD: 3.6) and 3.0 years (SD: 1.4), respectively. Severe regression (score of 1) in speech, motor, and cognitive function was found at an average age of 5.7 (SD: 2.7), 9.9 (SD: 4.3) and 8.2 (SD: 3.7) years, respectively. Speech was lost (score of 0) at an age of 8.2 (SD: 3.1) years. Loss of motor and cognitive functions was observed at an average age of 12.4 (SD: 5.3) and 13.1 (SD: 4.2) years, respectively. Scoring profiles for speech in patients with MPS IIIB were similar to those of the patients with MPS IIIA. Motor and cognitive functions in the patients with MPS IIIB started declining at ages similar to those of the patients with MPS IIIA; however, the average age of loss of these functions was reported 5.6 and 5.5 years later, respec-

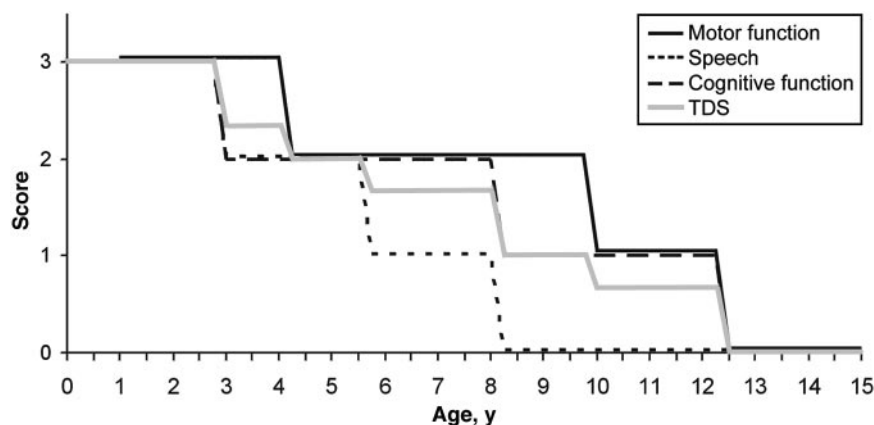
TABLE 4 First Symptoms Observed by Parents of Patients With MPS IIIA (N = 71)

First Symptom ^a	n (%)
Sleep disturbances	27 (38)
Behavioral abnormalities	27 (38)
Diarrhea	22 (31)
Recurrent infections	16 (23)
Speech delay	14 (20)
Hernia	14 (20)
Motor function delay	13 (18)
General developmental delay	10 (14)
Skeletal abnormalities	9 (13)
Coarse facial features	7 (10)
Delay in cognitive development	5 (7)

^aMultiple answers were permitted.

FIGURE 1

Regression of abilities as assessed by the FPSS (0–3) divided into average age score for motor function, speech, cognitive function, and the TDS of the MPS IIIA study population ($N = 71$).



tively, than in the patients with MPS IIIA. The loss of all 3 of the assessed abilities, as measured by the TDS, was observed at an average age of 12.5 years (range: 8.0–26.5) in patients with MPS IIIA. In a small group of patients with MPS IIIA (9.9%) >12.5 years (4 male and 3 female), speech, motor, and cognitive skills were partially preserved (minimum score of 1 in all of the assessed abilities) to a maximum age of 23.8 years, indicating a slower progression of the disease.

Developmental Regression

One third of the patients with MPS IIIA showed developmental regression before 4 years of age and 78.9% before 6 years of age. The first abilities in which regression were noticed were speech (67.6% of patients) and mental/cognitive abilities (42.3% of patients).

Age at Death

Eight of the patients with MPS IIIA (and 2 with subtype B) had died at the time of data collection. The median age at the time of death was 15.2 years (SD: 5.6 years [range: 8.5–25.5 years]).

DISCUSSION

The present study provides a detailed description of the natural course of MPS III. This report summarizes statistically relevant data on the age of onset, symptoms, diagnosis, and progression of the disease in 71 patients with MPS IIIA. Patient numbers for other subtypes were not large enough to produce statistically relevant data. Baehner et al² reported on the incidence of MPS III in Germany by the diagnosis of 211 patients with MPS III between 1980 and 1995 composed of subtype A (149, corresponding with 71%), B (49, corresponding with 23%), and C (13, corresponding with 6%). Numbers and the distribution of subtypes were consistent with the data assessed in this study. Furthermore the present study seems to cover ~40% of all of the patients with

MPS III in Germany. Studies using a scoring system for other neurodegenerative lysosomal diseases have been conducted for late infantile and juvenile neuronal ceroid-lipofuscinosis.^{20,21} The FPSS is an reliable and valid instrument, which can measure and document the course of the disease in MPS III. It is easy to use and provides important results concerning the clinical phenotypes and progression of disease. The majority of the patients with MPS IIIA (80%) were born after uneventful pregnancies. There were, however, a surprisingly high number of miscarriages observed in mothers of patients with MPS IIIA (19 of 65 women, corresponding with 29%). The general incidence of miscarriage is age dependent, and miscarriages are found in 10% of 20- to 24-year-old and 15% of 30- to 34-year-old women.²⁷ Because the exact age of the patients' mothers at the time of miscarriage is unknown, and no further investigations (eg, chromosomal testing) were conducted, it remains unclear whether the increased rate of miscarriages is related to MPS IIIA. At present, there are no reports of an increased risk of miscarriage in pregnancies involving children with lysosomal storage disorders in the literature. The majority of the patients with MPS IIIA (68%) first presented symptoms of the disease, mainly sleep disturbances and behavioral abnormalities, within the first year of life (Table 4). Patients with MPS IIIB presented first symptoms at a similarly early age. Only 10% of the patients with MPS IIIA presented with coarse facial features as a first symptom in contrast to ~30% of the patients with MPS IIIB. Our data showed that three quarters of children with MPS IIIA demonstrated delays in early developmental milestones (Table 3), the most common being a delay in speech development (67%). Speech delay was equally common in patients with MPS IIIB, but motor developmental delay was more common than in patients with MPS IIIA (33% [type A] vs 50% [type B]). Initial diagnosis in patients with MPS IIIA and B was made at an average age of 4.5 years, most probably because of developmental regression first presenting at this age. One third of patients were diagnosed after

5 years of age. We, therefore, suggest that every child with an unspecified developmental delay, behavioral abnormalities, or a delay in speech development should be tested for MPS III. The clinical course of the disease, measured by the TDS, varied substantially between patients in terms of both the age of onset and progression of the disease. Single scoring curves for motor function, speech abilities, and cognitive function revealed that deterioration in motor function, speech, and cognitive function (score of 2) was observed at an average age of between 2.6 and 4.1 years. Loss of speech (score of 0), however, was observed between 4.4 and 4.9 years earlier than loss of motor function and cognitive function. Speech, motor function, and cognitive skills were lost at a mean age of 12.5 years. In a small population of patients >12.5 years (9.9%), however, speech and motor skills were partially preserved (minimum score of 1 in all of the assessed abilities) to a maximum age of 23.8 years. This indicates that the FPSS may be used to classify patients into groups with a rapid or slower course of the disease, which may have an important impact on parental counseling, as well as therapeutic interventions (eg, surgical procedures). One third of the patients with MPS IIIA who were involved in the study were never tested for heart disease. Although the majority of patients did not show significant heart disease with therapeutic consequences, it is important to check for heart valve disease, because it is an indication for endocarditis prophylaxis.

CONCLUSIONS

To our knowledge, this is the largest study conducted in patients with MPS IIIA and the first assessment of the natural course of the disease using a scoring system. The FPSS may be used to predict the possible course of the disease and might also be used as a basis for the evaluation of the effectiveness of future therapies.

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REFERENCES

- Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill; 2001:3421–3452
- Baehner F, Schmiedeskamp C, Krummenauer F, et al. Cumulative incidence rates of the mucopolysaccharidoses in Germany. *J Inherit Metab Dis*. 2005;28:1011–1017
- Emre S, Terzioğlu M, Tokatlı A, et al. Sanfilippo syndrome in Turkey: Identification of novel mutations in subtypes A and B. *Hum Mutat*. 2002;19:184–185
- Michelakakis H, Dimitrou E, Tsagaraki S, Giouroukos S, Schulpis K, Bartsocas CS. Lysosomal storage diseases in Greece. *Genet Couns*. 1995;6:43–47
- Cleary MA, Wraith JE. Management of MPS type III. *Arch Dis Child*. 1993;69:403–406
- Van de Kamp JJ, Niermeijer MF, von Figura K, Giesberts MA. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). *Clin Genet*. 1981;20:152–160
- Van Schrojenstein-de Valk HM, van de Kamp JJ. Follow-up on seven adult patients with mild Sanfilippo B-disease. *Am J Med Genet*. 1987;28:125–129
- Nyhan WL, Barshop BA, Ozand PT, eds. *Atlas of Metabolic Diseases*. 2nd ed. London, United Kingdom: Hodder Education; 2005:524–531
- Berger-Plantinga EG, Vanneste JA, Groener JE, van Schooneveld MJ. Adult-onset dementia and retinitis pigmentosa due to MPS III-C in two sisters. *J Neurol*. 2004;251:479–481
- Di Natale P. Sanfilippo B disease: a re-examination of a particular sibship after 12 years. *J Inherit Metab Dis*. 1991;14:23–28
- Gabrielli O, Coppa GV, Bruni S, Villani GR, Pontarelli G, Di Natale P. An adult Sanfilippo type A patient with homozygous mutation R206P in the sulfamidase gene. *Am J Med Genet*. 2005;133:85–89
- Miyazaki T, Masuda N, Waragai M, Motoyoshi Y, Kurokawa K, Yuasa T. An adult Japanese Sanfilippo A patient with novel compound heterozygous S347F and D444G mutations in the sulphamidase gene. *J Neurol Neurosurg Psychiatry*. 2002;73:777–778
- Scott HS, Blanch L, Guo XH, et al. Cloning of the sulphamidase gene and identification of mutations in Sanfilippo A syndrome. *Nat Genet*. 1995;11:465–467
- Sewell AC, Pontz BF, Benischek G. MPS type IIIC (Sanfilippo): early clinical presentation in a large Turkish pedigree. *Clin Genet*. 1988;34:116–121
- Beesley CE, Burke D, Jackson M, Vellodi A, Winchester BG, Young EP. Sanfilippo syndrome type D: identification of the first mutation in the N-acetylglucosamine-6-sulphatase gene. *J Med Genet*. 2003;40:192–194
- Tylki-Szymańska A, Czartoryska B, Górka D, Piesiewicz-Grzonkowska E. Type III D MPS (Sanfilippo D): clinical course and symptoms. *Acta Paediatr Jpn*. 1998;40:492–494
- Di Natale P, Villani GR, Di Domenico C, Daniele A, Dionisi Vici C, Bartoli A. Analysis of Sanfilippo A gene mutations in a large pedigree. *Clin Genet*. 2003;63:314–318
- Muschol N, Storch S, Ballhausen D, et al. Transport, enzymatic activity, and stability of mutant sulfamidase (SGSH) identified in patients with MPS type III A. *Hum Mutat*. 2004;23:559–566
- Yogalingam G, Hopwood JJ. Molecular genetics of MPS type IIIA and IIIB: diagnostic, clinical, and biological implications. *Hum Mutat*. 2001;18:264–281
- Kohlschütter A, Laabs R, Albani M. Juvenile neuronal ceroid lipofuscinosis (JNCL): quantitative description of its clinical variability. *Acta Paediatr Scand*. 1988;77:867–872
- Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. *Am J Med Genet*. 2002;112:347–354
- De Jong JG, Wevers RA, Laarakkers C, Poorthuis BJ. Dimeth-

- ylmethylene blue-based spectrophotometry of glycosaminoglycans in untreated urine: a rapid screening procedure for mucopolysaccharidoses. *Clin Chem.* 1989;35:1472–1477
23. Whiteman P, Young E. The laboratory diagnosis of Sanfilippo disease. *Clin Chim Acta.* 1977;76:139–147
 24. Steer P. The epidemiology of preterm labour. *BJOG.* 2005; 112(suppl 1):1–3
 25. World Health Organization Multicentre Growth Reference Study Group. WHO Motor Development Study: windows of achievement for six gross motor development milestones. *Acta Paediatr.* 2006;450(suppl):86–95
 26. Blackwell PB, Baker BM. Estimating communication competence of infants and toddlers. *J Pediatr Health Care.* 2002;16: 29–35
 27. Heffner LJ. Advanced maternal age: how old is too old? *N Engl J Med.* 2004;351:1927–1929

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