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ORIGINAL ARTICLE

# Natural history of Sanfilippo syndrome type A

**Dakota Buhrman · Kavita Thakkar · Michele Poe · Maria L. Escolar**

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**Abstract**
*Objective* To describe the natural history of Sanfilippo syndrome type A.
*Methods* We performed a retrospective review of 46 children (21 boys, 25 girls) with Sanfilippo syndrome type A evaluated between January 2000 and April 2013. Assessments included neurodevelopmental evaluations, audiologic testing, and assessment of growth, adaptive behavior, cognitive behavior, motor function, and speech/language skills. Only the baseline evaluation was included for patients who received hematopoietic stem cell transplantation.
*Results* Median age at diagnosis was 35 months, with a median delay between initial symptoms to diagnosis of 24 months. The most common initial symptoms were speech/language delay (48 %), dysmorphology (22 %), and hearing loss (20 %). Early behavioral problems included perseverative chewing and difficulty with toilet training. All children developed sleep difficulties and behavioral changes (e.g., hyperactivity, aggression). More than 93 % of the children experienced somatic symptoms such as hepatomegaly (67 %), abnormal dentition (39 %), enlarged tongue (37 %), coarse facial features (76 %), and protuberant abdomen (43 %). Kaplan-Meier analysis showed a 60 % probability of surviving past 17 years of age.
*Conclusions* Sanfilippo type A is characterized by severe hearing loss and speech delay, followed by a rapid decline in cognitive skills by 3 years of age. Significant somatic disease occurs in more than half of patients. Behavioral difficulties presented between 2 and 4 years of age during a rapid period of cognitive decline. Gross motor abilities are maintained during this period, which results in an active child with impaired cognition. Sleep difficulties are concurrent with the period of cognitive degeneration. There is currently an unacceptable delay in diagnosis, highlighting the need to increase awareness of this disease among clinicians.

## Introduction

Mucopolysaccharidosis (MPS) type III, also known as Sanfilippo syndrome, is a rare inherited disorder caused by deficiency of one of the four enzymes involved in heparan sulfate metabolism (Valstar et al 2008). The most severe form, Sanfilippo type A, is caused by insufficient heparan-N-sulfatase activity (van de Kamp et al 1981). As undegraded heparan sulfate accumulates in the lysosome, progressive neurodegeneration occurs, manifesting as developmental delays, behavioral problems, and sleep disturbances; other problems include recurrent infections, diarrhea, hearing impairment, and seizures (Meyer et al 2007). Eventually mental retardation becomes apparent, and the patient becomes increasingly immobile and unresponsive (Valstar et al 2008).

The prevalence of Sanfilippo syndrome has been estimated at 0.28 to 4.1 cases per 100,000 live births (Valstar et al 2008). Sanfilippo type A is the most common of the Sanfilippo disorders with the exception of South-East Europe, where Sanfilippo type B is the most prevalent (Baehner et al 2005). At least 77 mutations have been reported; however, genotype–phenotype correlations are not fully understood (Yogalingam and Hopwood 2001; Valstar et al 2010; Héron et al 2011). A recent study described mutations in which genotype and phenotype appear to be related; however, most of these mutations are private. Sanfilippo syndrome is divided into severe, intermediate, or attenuated phenotypes (Valstar et al 2010).

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D. Buhrman · K. Thakkar · M. Poe · M. L. Escolar (✉)
University of Pittsburgh and Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15213, USA
e-mail: maria.escolar@chp.edu

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Current treatments for Sanfilippo syndrome are primarily supportive. Disease-specific therapies under investigation include substrate reduction with the soy isoflavone genistein (Piotrowska et al 2011), enzyme replacement therapy (Crawley et al 2011), and hematopoietic stem cell transplantation (Prasad et al 2008). Several forms of gene therapy are also currently being tested in several animal models (Haurigot et al 2013; Langford-Smith et al 2012).

As with other rare diseases, knowledge about disease progression and variability in the absence of treatment is limited. Natural history studies are needed to the design of clinical trials, understand outcomes, evaluate comparative effectiveness among therapies and ultimately guide clinical decision making. The aim of our study is to describe physical characteristics, signs and symptoms and neurodevelopmental involvement over time. In this study we describe the clinical and behavioral features of 46 children with Sanfilippo syndrome type A evaluated over a 13-year period.

## Methods

This is a retrospective review of clinical data from 46 patients referred to the Program for the Study of Neurodevelopmental Function in Rare Disorders between January 2000 and April 2013. A standardized protocol was followed prospectively for all evaluations including the order in which these were administered. The protocol was developed to maximize the ability to successfully test the children while avoiding fatigue (Martin et al 2008). The multidisciplinary assessment was performed by a team of neurodevelopmental pediatricians, speech and language pathologists, developmental specialists, psychologists, audiologists, and physical therapists. The protocol included review of the child's medical and family history and physical and neurologic examinations. Standardized and validated tools for assessing cognitive, language, and adaptive skills were used for all children. The study was approved by the institutional review boards of the University of Pittsburgh and the University of North Carolina, Chapel Hill and informed consent was obtained from parents or guardian. The evaluations took approximately 4 to 6 hours and were performed at a single clinic. Outcomes were compared to the norms of typically developing children (Elliott 1990; Mullen 1995; Bruininks et al 1996; Folio and Fewell 2000; Zimmerman et al 2002; Semel et al 2003; Martin et al 2008).

*Statistical analysis* Survival was estimated by the Kaplan–Meier method. The Social Security Death Index was queried to search for any deaths that occurred after the patient's last evaluation. (http://search.ancestry.com). Clinical growth charts were created based on the published Centers for Disease Control growth charts (Kuczmarski et al 2002). Developmental growth charts were created plotting the age-equivalent score against actual age. Age-equivalent scores are well suited for longitudinal analysis in neurodegenerative disorders as they can be used to ascertain whether a child is gaining or losing skills over time.

## Results

*Patient characteristics* We evaluated 46 children (21 boys, 25 girls; five Hispanic, 41 white) with Sanfilippo syndrome type A. Eleven of the children were evaluated once a year, with mean number of visits of 2.6 (range 2–4). Of the 35 children (age range 0.9–13 years) who underwent baseline evaluations only, 19 subsequently had unrelated umbilical cord blood transplantation, and 16 were lost to follow-up.

*Diagnosis and initial symptoms* Initial symptoms of the disease appeared before 12 months of age in 18 children (40 %) and before 24 months in 34 children (74 %). The most common initial symptoms were speech/language delay (48 %), followed by dysmorphology (22 %), hearing loss (20 %), motor delay (13 %), developmental delay (11 %), behavior problems (9 %), somatic disease (7 %), and ear infections (4 %) (Table 1). The median age of initial symptoms was 17 months (range 0–36 months). Median age at diagnosis was 35 months (range 0.5–9.8 years), with a median delay between initial symptoms and diagnosis of 24 months (range 1–82 months). Of the 46 children evaluated, 19 children developed neonatal problems, and 20 mothers experienced complications with pregnancy. Of the 19 children who experienced neonatal problems, 12 developed respiratory problems (e.g., pneumonia, respiratory distress, tachypnea, bronchitis and persistent pulmonary hypertension of the newborn), nine developed jaundice, and eight had feeding problems. Of the 20 mothers who experienced pregnancy complications, 12 underwent cesarean section; failure to progress, macrocephaly, and breech position were the most common reasons for this procedure. Eleven mothers had complicated pregnancies due to hypertension, hemorrhage, hyperemesis

**Table 1** Frequency of the initial symptoms in patients with Sanfilippo syndrome type A

| Symptoms | Number of patients (%) |
|---|---|
| Speech language delay | 22 (48 %) |
| Dysmorphology | 10 (22 %) |
| Hearing loss | 9 (20 %) |
| Motor delay | 6 (13 %) |
| Global developmental delay | 5 (11 %) |
| Abnormal behaviors | 4 (9 %) |
| Somatic symptoms (enlarged liver, lungs, heart) | 3 (7 %) |
| Ear infections | 2 (4 %) |

gravidarum, or hyperthyroidism. Six cases of Sanfilippo syndrome were diagnosed because of family history. Median age at diagnosis for these children was 12 months (range birth–28 months).

*Growth and survival* Most children had measurements above the 50th percentile for height, weight, body mass index, and head circumference (Fig. 1). Eleven (24 %) of the 46 children had macrocephaly. Of the 46 children involved in the study, three (7 %) died during the course of the study. Results of Kaplan–Meier analysis show that the probability of surviving past 17 years of age is 60 % (Fig. 2).

*Audiology* Hearing loss was apparent in 8/11(73 %) of the children younger than 2 years and 40/44 (91 %) of the children between 2 and 7 years. Auditory brainstem response testing showed that most of the hearing loss was sensorineural in origin. Interestingly the older children with the milder phenotype did not experience hearing loss. Hearing loss was typically mild to moderate in severity (Table 2), and 21/46 children (46 %) wore hearing aids. This is slightly higher than a previous study (Valstar et al 2010), which reported hearing loss in 27/73 (37 %) of their patients. Otitis media was also common (91 %) in the present study. The median age at which ear infections first began was 12 months (range 1–48 months). Most of the children (91 %) had tympanostomy tubes placed in their ears at a median age of 24 months (range 4–56 months).

*Developmental progression* Cognitive function, adaptive behavior, expressive and receptive language, and motor development were evaluated for each patient (Fig. 3). The two patients with atypical trajectories displayed behaviors that were similar to those of the other children; however, they scored higher in the areas of adaptive behavior and expressive

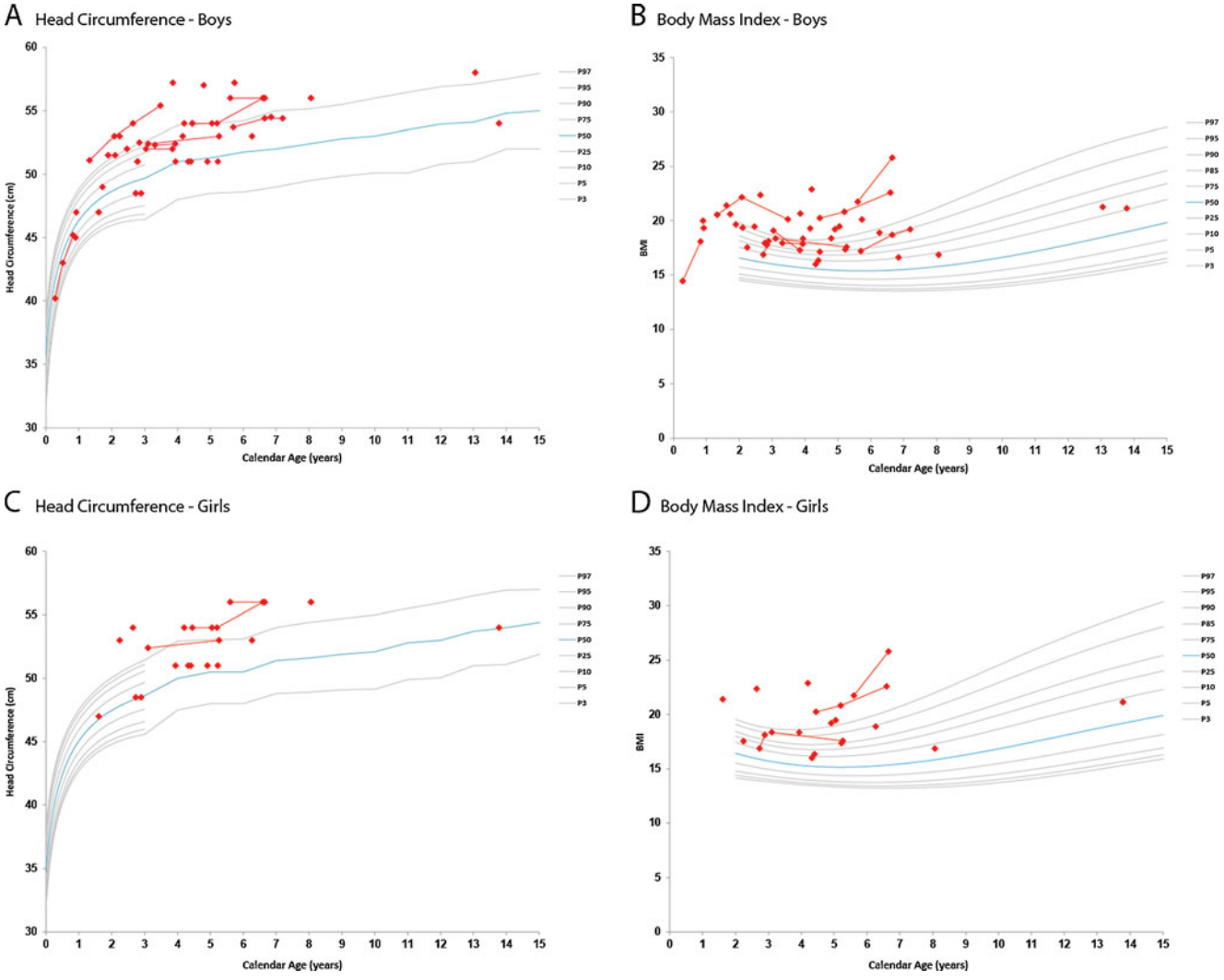


**Fig. 1** We measured body mass index and head circumference of boys and girls with Sanfilippo syndrome type A. Each red square depicts an individual measurement; lines connecting squares show multiple measurements for an individual child. The blue line represents the mean curve for typical developing children

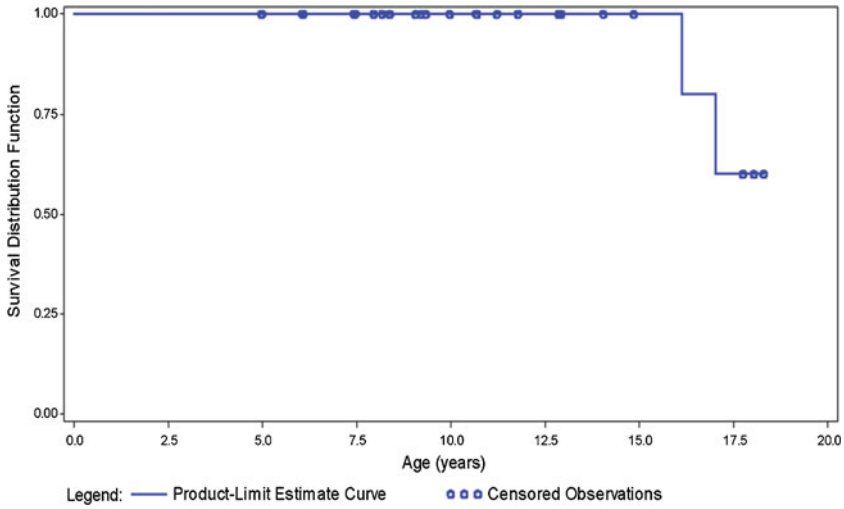


**Fig. 2** Kaplan–Meier survival curve. Kaplan–Meier analysis showed a 60 % probability of surviving past 17 years of age

language. Symptom onset occurred later for these two patients compared with the other patients.

*Receptive and expressive language* Language typically began to regress at 24 months of age, before overall cognitive decline was observed. Receptive language remained intact longer than expressive language (Fig. 3). Speech articulation problems were also apparent in 45 % of the children.

*Cognitive function* Cognitive function was the weakest area of development. This was assessed using standardized protocols that tested their ability to listen, solve visual problems, and perform simple tasks. Of the 11 patients followed longitudinally, only one (9 %) acquired new cognitive skills after the initial evaluation (Fig. 3).

*Adaptive behavior* Adaptive behavior remained intact longer than cognitive function. Eight of the 11 children followed longitudinally (73 %) acquired new skills in adaptive behavior between their initial and final visits. Toilet training and bowel control were the most affected adaptive skills. Five children were toilet trained (median age 4.8 years, range 3.9–5.6). A patient with the milder phenotype who was toilet trained at 13.7 years of age was excluded from the range since this child exhibited atypical adaptive behaviors that differed from those of the other children. Four of these children did not undergo follow-up evaluation, and one child lost this ability to control sphincters at 58 months. Of the 40 children who were never toilet trained, all had primary enuresis. Most of the children (85 %, 0.9–6.8 years of age) were able to eat independently when evaluated during the course of the study (Fig. 3).

**Table 2** Hearing loss in patients with Sanfilippo syndrome type A

| | < 2 years (n=11) | 2–3 years (n=20) | 4–6 years (n=24) | ≥7 years (n=2) |
|---|---|---|---|---|
| None | 3 (27 %) | 2 (10 %) | 2 (8 %) | 0 (0 %) |
| Mild | 1 (9 %) | 5 (25 %) | 9 (38 %) | 0 (0 %) |
| Mild–moderate | 6 (55 %) | 10 (50 %) | 7 (29 %) | 2 (100 %) |
| Moderate–severe | 1 (9 %) | 3 (15 %) | 6 (25 %) | 0 (0 %) |

Note: n = total number of patients

## Motor development

*Fine motor* For all children, deficits in fine motor skills became apparent between 2 and 3 years of age. Fine motor development mirrored cognitive development (Fig. 3).

*Gross motor* Gross motor was the strongest area of development until 5 to 6 years of age, when despite good motor skills, cognitive decline affected the child's ability to follow directions during motor testing, resulting in low scores. Balance was the most affected area of gross motor development (Fig. 3).

*Behavioral problems* Early behavioral signs and symptoms included hyperactivity, aggression, sleep difficulties, preservative chewing, and separation anxiety (Fig. 4). Many of the children woke in the middle of the night and had bouts of hyperactive behavior or experienced other sleep pattern disturbances. However, this behavioral pattern changed with time, and most became withdrawn as they lost mobility.

*Somatic symptoms* Most of the children in this study showed somatic signs and symptoms; the most common were coarse facial features (76 %), hepatomegaly (67 %), enlarged tongue (37 %), and abnormal dentition (39 %). Fifteen children had a history of umbilical hernia (33 %) with a mean age of 41 months (range 17–80 months), and six had a history of inguinal hernia (13 %) with a mean age of one month (range newborn–3 months). Thirty-three children (72 %) underwent a tonsillectomy, adenoidectomy, or both. The mean age at

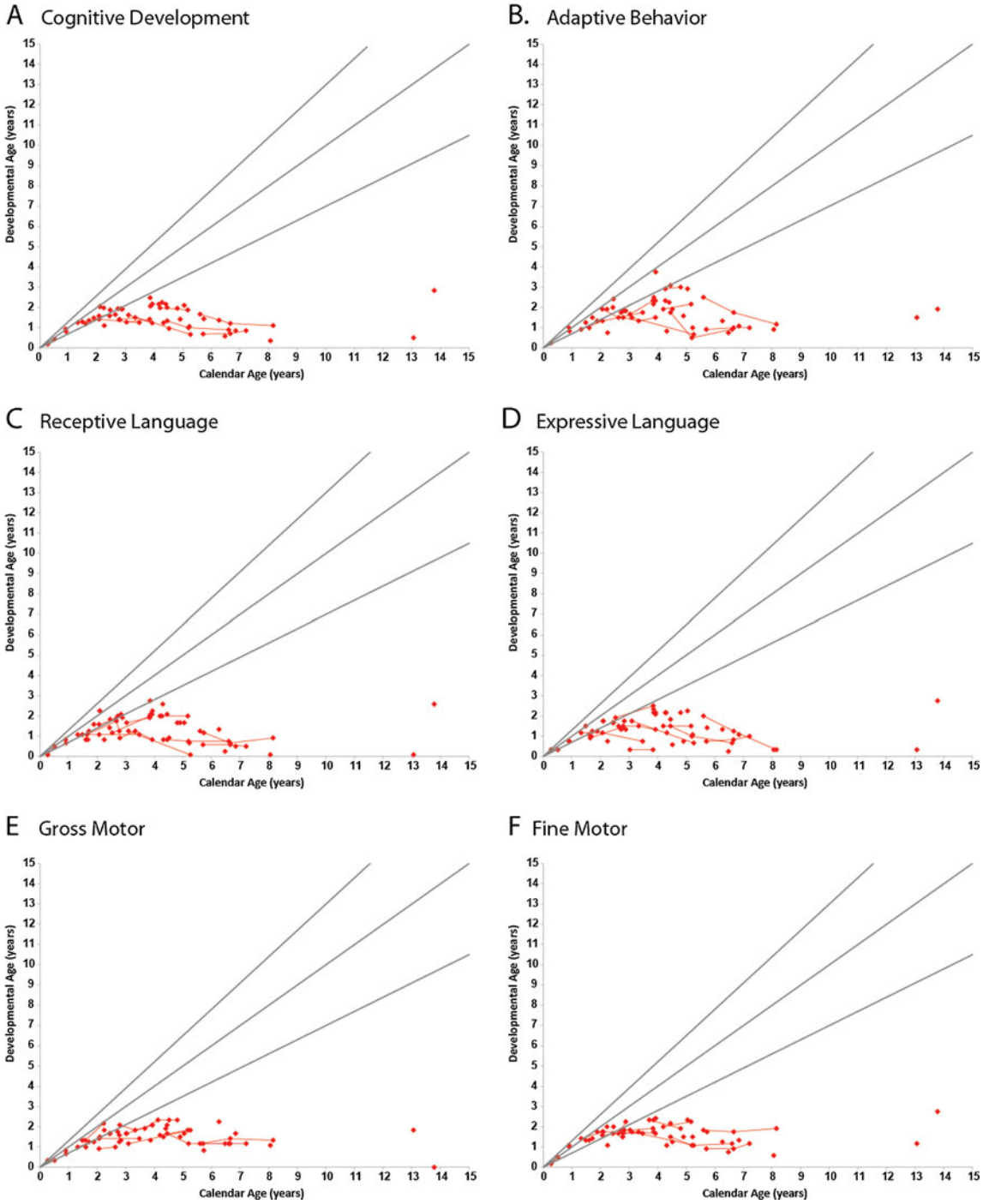


**Fig. 3** Developmental progression of children with Sanfilippo syndrome type A

which somatic symptoms first appeared was 12 months (range 4–18 months).

## Discussion

Sanfilippo type A is characterized by severe neurological involvement manifested by hearing loss and speech delay, followed by a rapid decline in cognitive skills by 3 years of age. Hearing loss occurs at a time of peak language development, which may be one of the reasons that language is affected before cognition. As previously reported, sleep difficulties began during the period of cognitive decline (Cleary and Wraith 1993). Behavioral difficulties present early in the disease progression, between 2 and 4 years of age, as they lose language and hearing followed by a decline in cognitive skills. During this time, functional evaluations are challenging because of the child's difficult behaviors and frustration at being

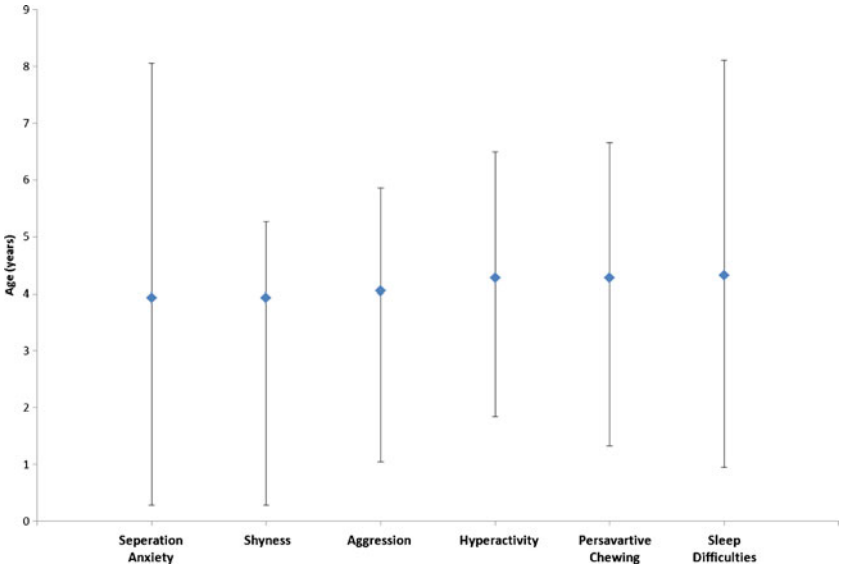


**Fig. 4** Ages at which common behavior difficulties were present in children with Sanfilippo Type A

unable to perform previously mastered skills. The evaluations require a highly skilled clinical team with disease-specific expertise. Consistent with results of a previous study (Malm and Mansson 2010), we found that gross motor abilities are generally maintained longer than other skills, which results in a motor-driven active child with impaired cognition. The increased activity was commensurate and normal for a child of a corresponding developmental age. However, the combination of hearing loss, speech and cognitive delay with stronger motor abilities and increased body mass makes people perceive these children as hyperactive and aggressive when in fact the behaviors are corresponding to the level of functioning. Interestingly, children's measurements including height, weight, and head circumference were above the 50th percentile, and some children were macrocephalic at birth. Forty-four of the children (96 %) were above the 50th percentile for body mass index. Many mothers required a cesarean section or had a difficult pregnancy, suggesting that the storage may be already occurring before birth. This finding needs to be investigated further as children are diagnosed earlier or identified through newborn screening.

With respect to developmental progression, two patients maintained skills at the one- to two-year level of function longer than the other 44 children. This could be due to differences in N-sulfoglucosamine sulfohydrolase (SGSH) gene mutations, as reported by Meyer et al (2008). In that cohort of 54 patients, the seven patients who progressed more slowly were found to have the p.Ser298Pro mutation. Unfortunately we were unable to perform genetic analysis in our patients to confirm this finding. In addition, ten patients received the natural supplement genistein during the course of the study; however, the supplement was given inconsistently and at different doses. Analysis of the data of these groups did not detect a difference between the children and those who did not receive supplement; therefore, children on genistein were not excluded from the study.

We found that 93 % of the children in our study showed significant somatic disease, irrespective of gender. This finding is consistent with results reported by van de Kamp et al (1981), Meyer et al (2007), and Héron et al (2011) but differs from those of Valstar et al (2010) and Malm and Mansson (2010). The strength of this study is that all children were evaluated in the same center using a pre-established clinical and neurodevelopmental protocol, which included standardized and validated assessments performed by specialists in each area of development. This protocol minimized error in observations and allowed for inexperience in testing this difficult-to-test population. Neurodevelopmental testing was performed in a specific order so that cognitive testing was done before motor testing to avoid hyperactivity, and medical evaluations, including physical and neurological examinations, were completed after or in combination with motor testing.

Our study indicates that, as with MPS I (Hurler syndrome) and MPS II (Hunter syndrome), both neurologic and somatic disease are prevalent in children with Sanfilippo type A syndrome; however, somatic manifestations are less apparent because of minimal bone and skeletal deformities. Better knowledge of the presenting symptoms of Sanfilippo type A will increase awareness of this disease among pediatricians and result in earlier diagnostic referrals. Several clinical trials are planned for the near future, requiring natural history studies to define endpoints and evaluate response to treatment. Identifying the developmental trajectory and behavioral phenotypes provides information that can help design meaningful endpoints for future therapies. Behavioral and sleeping difficulties are the most challenging problems reported by

families. Further studies are needed to understand the etiology of behavioral and sleep difficulties that severely impact the quality of life for these children and their families.

Limitations of this study include the inability to correlate behavioral data with genetic mutations, which were not available for most patients, and the limited follow-up in 35 of the patients since 16 were lost to follow-up, and 19 subsequently underwent umbilical cord blood transplantation (data not included in longitudinal analysis). Consequently, the baseline data was only analyzed cross-sectionally.

**Competing interest** Dr. Escolar is a consultant for Shire Human. The content of the article has not been influenced by the sponsors.

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