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Activities of Daily Living in patients with Hunter syndrome: Impact of enzyme replacement therapy and hematopoietic stem cell transplantation

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Compliance with Ethics

The study was approved by the Institutional Review Boards (IRB) at Gifu University, at Saint Louis University, and at Nemours/Alfred I. duPont Hospital for Children.

Conflict of Interest:

All the authors contributed to the Original Article and have no conflict of interest with any other party.

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Contributions to the project:

Julian Tanjuakio contributed to the planning, data analysis, and reporting of the work described.

Yasuyuki Suzuki is a Principal Investigator for this project and has contributed to the concept, treatment of patients, planning of the project, informed consent, analysis of data, and reporting of the work described. He and his team conducted the project and followed up with the patients.

Pravin Patel has contributed to the planning, data analysis, and reporting of the work described.

Francyne Kubaski has contributed to the planning, data analysis, and reporting of the work described.

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Toshiyuki Fukao has contributed to the treatment of patients and the planning, data analysis, and reporting of the work described. He and his team conducted the project with Y. Suzuki.

Tadao Orii has contributed to the planning, data analysis, and reporting of the work described.

Shunji Tomatsu is a Principal Investigator for this project and has contributed to the concept and planning of the project, analysis of data, and reporting of the work described. He and his team conducted the project with Dr. Suzuki.

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Abstract

The aim of this study was to assess the Activities of Daily Living (ADL) in patients with Hunter syndrome (mucopolysaccharidosis II; MPS II) using a newly designed ADL questionnaire. We applied the questionnaire to evaluate clinical phenotypes and therapeutic efficacies of enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). We also explored early signs and symptoms to make early diagnosis feasible.

We devised a new ADL questionnaire with three domains: “Movement,” “Movement with Cognition,” and “Cognition.” Each domain has four subcategories rated on a 5-point scale based on level of assistance. We also scored signs and symptoms unique to MPS by 12 subcategories (five points per category), providing 60 points in total. The questionnaire was first administered to 138 healthy Japanese controls (0.33 – 50 years), and successively, to 74 Japanese patients with Hunter syndrome (4 – 49 years). The patient cohort consisted of 51 severe and 23 attenuated phenotypes; 20 patients treated with HSCT, 23 patients treated early with ERT (< 8 years), and 25 patients treated late with ERT (> 8 years), and 4 untreated patients. Among 18 severe phenotypic patients treated by HSCT, 10 were designated as early HSCT (< 5 years), while 8 were designated as late HSCT (> 5 years).

Scores from patients with severe phenotypes were lower than controls and attenuated phenotypes in all categories. Among patients with severe phenotypes, there was a trend that HSCT provides a higher ADL score than early ERT, and there was a significant difference in ADL scores between late ERT and HSCT groups. Early ERT and early HSCT provided a higher score than late ERT and late HSCT, respectively.

In conclusion, we have evaluated the feasibility of a new questionnaire in control population and patients with Hunter syndrome, leading to a novel evaluation method for clinical phenotypes and therapeutic efficacy. Early treatment with HSCT provides a better consequence in ADL of patients.

Keywords

enzyme replacement therapy; hematopoietic stem cell transplantation; activities of daily living; Hunter syndrome; clinical phenotype

1. Introduction

Hunter syndrome (mucopolysaccharidosis II; MPS II) is an X-linked recessive lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS). IDS is required for the degradation of the glycosaminoglycans (GAGs), dermatan sulfate (DS) and heparan

sulfate (HS). Deficiency of this enzyme results in the accumulation of GAG in most cell types and tissues, leading to the progressive damage to the bone, cartilage, upper and lower respiratory tract, lung, heart, and brain. Clinical manifestations include coarse facial feature, umbilical hernia, inguinal hernia, marked Mongolian spots, obstructive airway disease, recurrent nose and ear infections, and skeletal deformities [1]. Patients commonly show initial excessive growth in the first few years followed by growth retardation, umbilical hernia, inguinal hernia, and thick bones [1]. In Asian populations, an early sign is appearance of a prominent Mongolian spot [2]. Ultrastructural findings of Mongolian spots suggest that the hyperpigmentation is a long-lasting symptom. Detection of Mongolian spots may lead to early diagnosis in patients with a mild form of Hunter syndrome [2].

Clinical cases of Hunter syndrome are ranked on a continuum from attenuated phenotypes to severe phenotypes. Severe and attenuated phenotypes are differentiated by the presence or absence of cognitive impairment. The severe phenotype of Hunter syndrome, which is twice as prevalent as the attenuated form, is characterized by significant CNS involvement such as mental retardation and loss of cognitive function [3–7]. Untreated patients usually do not survive past their second decade of life [1,3]. Patients with attenuated phenotypes are mainly characterized by somatic involvement without CNS involvement. Surgical operations of umbilical/inguinal hernia repair, tonsillectomy, adenoidectomy, and ear tubes are common in Hunter syndrome [1,8,9]. Risk factors of mortality in patients with Hunter syndrome include severe upper airway constriction and abnormal heart development causing left and right ventricular hypertrophy, heart valvular involvement, and heart failure [1, 9].

Although there is no cure for Hunter syndrome, current treatments include enzyme replacement therapy (ERT) [10,11] and hematopoietic stem cell transplantation (HSCT) [6,7], to reduce the accumulation of GAG. Studies have shown that ERT can reduce GAG levels in both urine and plasma, improve lung, heart, and other visceral organ function, and prolong a patient's life. However, limitations of ERT result from 1) its high cost, 2) inability of the enzyme to cross the blood-brain barrier, 3) the need for weekly infusion for 4 – 5 hours at a medical facility, and 4) limited impact on CNS, avascular cartilage, and the skeletal system [9]. HSCT has proved to be similar to or better than ERT in terms of reduction of GAG levels and organ function [6,7]. Previous studies have shown beneficial therapeutic effects of ERT and HSCT on growth in patients [6,7] but a comparison of the relative benefits of ERT and HSCT on Activities of Daily Living (ADL) has not been reported previously. Gene therapy for Hunter syndrome and substrate reduction therapy (SRT) for MPS in general are potential alternative treatments that are currently in clinical trials [12,13]. Regardless of treatment mode, early treatment yields the most significant impact in ameliorating disease symptoms [5–7]. Newborn screening for Hunter syndrome is now under development [8,14].

To assess the ADL and other clinical endpoints, patients and their families with Hunter syndrome have taken several tests and completed a range of questionnaires. The Functional Independence Measure (FIM) is widely used to evaluate ADL in patients with a range of disabilities [15], including Hunter syndrome [4,5,16]. Originally designed for patients with neurological disorders such as dementia and multiple sclerosis, the FIM questionnaire tests the patients on motor and cognitive function. The need for a trained professional to

administer the questionnaire makes the assessment inconvenient and time consuming for the family and patients. Other types of questionnaires used to evaluate ADL in Hunter syndrome patients include The Hunter syndrome-functional outcomes for clinical understanding scale (HS-FOCUS) [17,19], and Pediatric evaluation of Disability inventory (PEDI) for general child health [16]. To date, only a few studies have evaluated the clinical status of Hunter syndrome [9, 14–18], and the effect of ERT and HSCT on ADL in patients with Hunter syndrome has not been reported yet.

In this report, we have created a new, simple ADL questionnaire that can be easily completed by patients or their parents. We have evaluated its value using normal control subjects, showing increased ADL in older children. Successively, we showed that responses to the questionnaire can separate MPS II patients from age-matched healthy controls, and also distinguish patients with severe and attenuated phenotypes. We have applied this questionnaire to compare the impact of ERT and HSCT on ADL.

2. Subjects and Methods

2.1. Study subjects

All control and Hunter syndrome patients were of Japanese ethnicity and were enrolled, with informed consent at local Japanese hospitals. Normal control subjects ($n = 138$; 75 males, 63 females; age range 0.33 – 50 years old; average age, 8.34 ± 7.75 years) and patients with Hunter syndrome ($n = 74$; age range, 3 – 47 years old; average age 17.27 ± 8.69 years) were enrolled. Fifty-one patients were diagnosed with severe phenotypes (diagnosed mean age; 3.09 ± 1.57 years), and 23 patients were diagnosed with attenuated phenotypes (diagnosed mean age; 4.4 ± 2.03 years). Twenty-three patients were treated with early ERT alone (treatment before the age of 8 years), 25 patients were treated with late ERT alone (treatment after the age of 8 years), 12 patients were treated with HSCT alone, 8 patients were treated with both ERT and HSCT, and 4 patients were untreated. The average age at which patients started treatment using ERT was 5.2 ± 2.2 years for early-stage group and 17.8 ± 6.6 years for the late-stage group. The average age at which patients started treatment using HSCT was 3.6 ± 1.1 years for early-stage group (before 5 years of age) and 5.9 ± 1.6 years for the late-stage group (after 5 years of age).

Average age of treatment was 4.8 ± 1.6 years for HSCT-treated patients. Average time since HSCT had been performed was 10.6 ± 9.49 years, and average since ERT was 6.0 ± 2.0 years.

2.2. Questionnaire

The questionnaire (12 items) used (see Supplement Fig. 1) consisted of three domains (“Movement,” “Movement with Cognition,” and “Cognition”); each with four subcategories scored from 0 – 5, 0 being the inability to perform task without maximum assistance, and 5 being the ability to perform a task without any assistance. “Movement” comprised basic motor skills needed for normal daily function with the subcategories: 1) walking, 2) movement on stairs, 3) grasping/finger movement, and 4) endurance in a 6-minute walk (6 MWT). “Movement with Cognition,” daily activities that required some level of cognitive awareness, comprised 1) toileting, 2) changing clothes, 3) bathing, and 4) eating. For

“Cognition,” subcategories included 1) understanding of everyday conversation, 2) conversation and speaking with others, 3) social participation, and 4) problem solving. The maximum possible score that could be obtained was 20 per domain with a total of 60 points.

In a second section of the questionnaire, twelve other symptoms specific to MPS were assessed including: work/study, behavioral problems, sleep, pain, joint flexion, respiratory status, infection, vision, hearing, skin, hair, and appetite. These were all scored on 0 – 5 scales.

In a third section, patients and their parents were asked about growth (birth, 1.5 years, and 3 years), initial and early signs and symptoms of Hunter syndrome, and surgical history (Fig. 1).

Questionnaires were mailed to families, completed directly by the patient and/or the patient’s parent/guardian, and then returned to the study group.

2.3. Statistical Analysis

Means and standard deviations of the total score and each domain were calculated by age groups 0 – 5, 5 – 10, 10 – 15, and > 15 years of age. Student’s *t*-test was used to compare the means of 1) the patients with Hunter syndrome to age-matched normal controls, 2) patients with the severe phenotypes to patients with attenuated phenotypes, 3) ERT patients to HSCT patients, 4) early ERT or HSCT patients to late ERT or HSCT. Most patients were classified as severe, and, therefore, there was insufficient data to compare treatments for patients with an attenuated phenotype.

Statistical analysis—Statistical analyses were performed using Student *t*-test with SPSS v.16. The significance level was set at $p < 0.05$.

3. Results

3.1. Early Signs and symptoms

The reported initial signs and symptoms included bone deformity, failure of thrive, kyphosis, scoliosis, abnormal gait, difficulty of joint movement, herniation, knee problem, corneal clouding, chronic ear infections, short neck, and heart murmur (Fig. 1). At early stages of the disease, patients were frequently found to have inguinal hernia, umbilical hernia, prominent Mongolian spot, and thick bones (Table 1). Early signs and symptoms, including extensive Mongolian spots, did not distinguish severe and attenuated phenotypes. Inguinal hernia repair (53%), ear tub (49%), and adenoidectomy (32%) were the most frequent surgical procedures in both phenotypes (Table 1).

Excessive growth at an early age was noticed in Hunter syndrome patients. Birth weights and lengths of patients were near normal, but by aged 1.5 and 3 years, 30% and 15% respectively had both weight and height above the 97th percentile, confirming excessive growth in Hunter syndrome patients (Table 1). More than 50% of patients had weights above the 97th percentile of the normal population at both ages.

3.2. ADL Scores in Control Subjects

3.2.1. Total scores—In control subjects, all scores increased with age (Fig. 2). The total score reached a plateau at around 10 years of age and all control subjects older than 15 years of age obtained a maximum score (Fig. 2a).

“Movement” scores reached a plateau at around 7 years of age (Fig. 2b) and “Movement with Cognition” scores reached a plateau at about 8 years of age (Fig. 2c). “Cognition” scores developed more slowly, reaching a plateau at 11 years of age (Fig. 2d).

3.3. Comparison of ADL scores between controls and patients with a severe or attenuated phenotype

Total scores for patients with a severe phenotype ranged from 0 to 43 (Fig. 3a). Unlike control subjects, scores decreased with age for these patients. Cognitive function showed the greatest decline with age in these patients. Twenty-five of 35 patients more than ten years old had a cognition score of 5 or less. The mean score was significantly lower than that of the age-matched controls across all domains and age groups for these severe phenotypic patients (Table 2).

In patients with an attenuated phenotype, total scores increased with age, similar to that of control subjects (Fig. 3a). These patients had almost perfect scores between 15 and 30 years of age, but the two older patients had lower scores than controls. Patients with attenuated phenotypes had significantly higher scores than patients with severe phenotypes, in all categories and across all age groups (except for patients aged 0 – 5 in the Movement domain) (Table 2, Supplemental Fig. 2).

Among other symptoms related to MPS, patients with a severe phenotype had lowest scores in behavioral problems and joint flexion and also had low scores in hair and skin quality and work/study habits (Supplemental Fig. 3). Patients with an attenuated phenotype had better scores than severe phenotype patients for all symptoms apart from joint flexion (Supplemental Fig. 3).

3.4. ADL scores in ERT vs HSCT patients

Table 3 shows a comparison of severe phenotypic patients who had been given HSCT, early ERT, or late ERT. In patients with a severe phenotype treated by HSCT ($n = 18$; mean present age 12.69 ± 5.17 years), the overall average score was 27.9 ± 11.4 , and scores were similar in all age groups. Lower scores were generally seen in toileting, conversation, and problem solving subcategories (Fig. 4).

For severe phenotypic patients who started ERT at an early age ($n = 16$; mean present age 10.1 ± 3.7 years), the overall average score was 21.6 ± 9.0 . Average scores in each domain and age group were lower than in the HSCT group, but were not statistically different.

Late ERT patients ($n = 13$; mean present age 19.8 ± 5.2 years) had lower scores than the HSCT and early ERT treatment groups (mean score 9.5 ± 10.5 , Table 3). Nine out of 13 (70%) patients had less than 10 points.

The five highest scores among treated groups were obtained by HSCT-treated patients while the lowest score (0) was obtained by three late ERT patients (Fig. 3b). The highest scores for both treatment types were seen in hand movement and walking (Fig. 4).

3.5 Early treatment with HSCT

The early HSCT group, treated before 5 years of age ($n = 10$; mean age at analysis 11.3 ± 5.2 years), scored 33 ± 7.0 while late HSCT group ($n = 8$; mean age 13.3 ± 4.7 years) scored 21.2 ± 13.0 ($p < 0.05$). The 4 HSCT patients with less than 20 points were in the late HSCT group. Scores in all three domains were higher in the early HSCT group than those in the late HSCT group; “Movement” (17.3 ± 2.8 vs 12.4 ± 6.2), “Movement with Cognition” (10.9 ± 4.1 vs 5.8 ± 3.4), and “Cognition” (4.8 ± 2.0 vs 3.4 ± 3.9). Two patients diagnosed as severe phenotype Hunter syndrome were treated with HSCT at 2 years of age. They were 3 and 17 years old at the time of this study. The 3-year-old patient obtained a score of 26, relatively normal compared to age-matched controls. The 17-year-old patient obtained a score of 42, which is amongst the highest for patients with a severe phenotype.

4. Discussion

Hunter syndrome is a progressive systemic disease of the CNS and the skeleton that has a serious impact on the daily activities of patients and their families. Therefore, characterizing the ADL will provide a better understanding of the obstacles for patients with Hunter syndrome, thereby enabling physicians to evaluate therapeutic efficacy and parents/families to understand the progression of the patient’s quality of life.

Traditional questionnaires such as the FIM, HS-FOCUS, and PEDI have been used to evaluate ADL for patients with Hunter syndrome [16 – 18]. These questionnaires are limited by their age requirements, time consumption, complexity, and the requirement for professional examiners. We have developed a new questionnaire to characterize ADL in patients with Hunter syndrome. This new questionnaire, containing just 12 items total, is concise and simple enough so that patients and their families can self-assess without the need of a trained individual. The questionnaire also maintains sensitivity to age, disease, and phenotype, creating a holistic image of the ADL, covering a broad spectrum of daily activities from motor skills to cognitive function. Distinct from other ADL questionnaires, the body of this questionnaire is divided into three domains of “Movement,” “Movement with Cognition,” and “Cognition.” These three domains are suitable for evaluating Hunter syndrome, in which both somatic and CNS manifestations are present.

Furthermore, since patients suffer from difficulties in their environment, it is important to assess not only impairment but functionality [14]. As a result, this questionnaire scores the level of assistance the patient requires, resulting in a more precise evaluation of ADL. A sample size of 74 is the largest population of Japanese Hunter syndrome patients examined in an ADL study to date, in part due to its simplicity and suitability for evaluation of Hunter syndrome.

This study has evaluated the feasibility of this new questionnaire. Examination of the questionnaire data has demonstrated that 1) the questionnaire can distinguish patients with

Hunter syndrome from age-matched controls, 2) the questionnaire can distinguish clinical phenotypes between “severe” and “attenuated,” 3) early HSCT and ERT yield higher scores than late ERT and HSCT, respectively, and 4) early HSCT provides the highest score among treatment groups.

The scores of the age-matched controls were higher than those of patients with the severe phenotype of Hunter syndrome, and the difference in scores increased with age. This questionnaire has also shown that there is a significant difference between the severe and attenuated phenotypes in all domains. However, due to limited respondents, no comparison between the two phenotypes could be made in the 0 – 5 years age group. Our results are consistent with the current understanding that patients with severe phenotypes have more significant CNS involvement than patients with attenuated phenotypes who primarily have somatic involvement (Tables 1 and 2).

Although patients with attenuated phenotypes are characterized as showing perseveration of cognitive ability, the two older patients in this phenotype, aged 40 and 47 years, had low cognitive scores. This declining cognitive ability may be due to the severe hearing and visual impairment in these two patients, rather than a direct reduction in cognitive function. A larger cohort of older patients will be needed to determine whether a decline in cognitive score is feature of patients with attenuated Hunter syndrome.

An essential use of ADL questionnaires is to assess therapeutic efficacy and how certain treatments can improve the status of the patient’s ADL. In this study, treatment groups were HSCT, early ERT, and late ERT. Several treated patients had been diagnosed as attenuated phenotype. Only severe phenotype patients were included in the treatment analysis because the attenuated phenotype patients would have likely scored high with or without treatment. HSCT patients could be divided into early and late treatment groups but as patients in the two sub groups spanned similar age ranges, they were pooled to enable better statistical analysis. For ERT, it has become more common to begin treatment at an early age and consequently early and later ERT treated patients span different age groups and consequently can be analyzed separately with little loss of statistical power. The only groups for which statistically significant differences could be obtained was for patients older than 15 years of age showing better scores in HSCT treated patients than late ERT treated patients in “Movement” and “Movement with Cognition” (Table 3). However, the oldest HSCT treated patient in this study was 18 years old while the mean age of the late ERT group was over 20 years old. Nevertheless, all of the early HSCT treated patients score in the top half of all treated patients and longer term follow up studies on the progress of these patients appear likely to show better outcomes for early HSCT. Although ADL scores of patients treated with HSCT were not statistically different from those treated with early ERT, average scores were higher for the HSCT treated patients for each domain and each age group (Table 3). While “Movement” and “Movement with Cognition” scores appear to be stable across age groups for HSCT treated patients, Cognition scores remain low for HSCT treated patients. If patients could be diagnosed at birth through newborn screening, earlier treatment may be possible to help overcome reduced cognitive development in Hunter syndrome patients.

Our recent study on the blood HS level in patients with Hunter syndrome [20] showed 1) a significant increase in untreated patients with a severe form compared with the age-matched control group, 2) a significant increase in patients with a severe form compared to those with an attenuated form, 3) a significant decrease in the ERT- or HSCT-treated group compared with that in the untreated group, 4) a further reduction in patients treated by HSCT compared with patients treated by ERT. These results using HS as a biomarker are consistent with the better outcomes shown for HSCT patients in this current study. In future studies it will be of great interest to explore whether differences in blood HS levels are associated with ADL in patients with Hunter syndrome with or without treatment (or type of treatment).

In addition to the ADL, we also investigated early signs and symptoms of patients with Hunter syndrome since early diagnosis and early treatment are critical to improve quality of life. It is noteworthy that excessive growth, hernia, prominent Mongolian spot, or thick bone is observed during early stages of Hunter syndrome, and that recognition of these early signs and symptoms leads to early diagnosis. Excessive growth at a young age is also a feature of some other types of MPS [21,22]. During the first 4 years of life, the mean height for Japanese patients with Hunter syndrome is higher than that of an age-matched control population [22]. Clinical severity of CNS involvement in patients does not correlate with severity of growth impairment [21,22]. The etiology of the initial rapid growth followed by impairment of growth is not fully understood. Stimulation of the endocrine system for growth and other factors at an early stage could contribute to the early rapid growth. Further study of hormonal effect is needed to understand the mechanism of this early rapid growth.

In conclusion, we have determined the reliability of this questionnaire to show that it can distinguish the control subjects from the patients with Hunter syndrome and patients with severe phenotypes from attenuated phenotypes. We have also compared therapeutic efficacy, confirming the benefit of early treatment. HSCT provides a favorable consequence compared with ERT, although a significant difference between HSCT and early ERT remains to be supported. Moreover, future ADL evaluation of other MPS types or lysosomal storage disorders can be determined by using this questionnaire.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlight

- A simple and novel questionnaire is evaluated to assess ADL for a control population and patients with Hunter syndrome.
- ADL questionnaire distinguishes Hunter syndrome patients from age-matched controls
- ADL questionnaire distinguishes the severe and attenuated phenotypes of Hunter syndrome.
- Significant difference in ADL is present between patients treated with HSCT and late ERT.
- Early HSCT provide a higher ADL score than late HSCT.

Figure 1.
Initial signs and symptoms of patients with Hunter syndrome (n = 73)

a)

b)

Figure 2. ADL score for control subjects (n = 138; 4 months – 50 years). a) total score, b) “Movement,” c) “Movement with Cognition,” d) “Cognition.”

Figure 3.

ADL score for patients with Hunter syndrome

a) Total ADL score for patients with severe (n = 50; 3 years – 29 years) or attenuated (n = 23; 6 years – 47 years) phenotypes.

b) Total ADL score of patients with severe phenotypes by treatment type. Early ERT (n = 16); Late ERT (n = 13); Early HSCT (n=10); Late HSCT (n = 8).

Figure 4.

Profile of subcategory scores for patients by treatment and age group

- a) 0 years – 5 years: Control (n = 46); Early ERT (n = 3); severe (n = 4).
- b) 5 years – 10 years: Control (n = 54); Early ERT (n = 3); HSCT (n = 7); severe (n = 10); attenuated (n = 4).
- c) 10 years – 15 years: Control (n = 25); Early ERT (n = 9); HSCT (n = 4); severe (n = 15); attenuated (n = 8). Late ERT (n = 2) is not shown due to low number of patients.
- d) > 15years: Control (n = 13); Late ERT (n = 11); HSCT (n = 7); severe (n = 21); attenuated (n = 13). Early ERT (n = 1) is not shown due to low number of patients.

Table 1

Growth pattern, early signs and symptoms, and surgical operations.

		Attenuated	Severe
N		23	51
Age (Years)		20.22 ± 10.45	13.67 ± 6.07
Height above 97th percentile	Birth	5%	4%
	1.5 years	17%	38%
	3 Years	18%	13%
Weight above 97th percentile	Birth	5%	10%
	1.5 Years	44%	63%
	3 Years	29%	63%
Height OR Weight above 97th percentile	Birth	10%	10%
	1.5 Years	50%	65%
	3 Years	35%	63%
Height AND Weight above 97th percentile	Birth	0%	6%
	1.5 Years	33%	35%
	3 Years	18%	13%
Early Symptoms	Umbilical Hernia	26%	16%
	Inguinal Hernia	17%	26%
	Mongolian Spot	91%	61%
	Thick Bone	57%	54%
Operations	Umbilical Hernia	26%	14%
	Inguinal Hernia	61%	49%
	Tonsillectomy	17%	20%
	Adenoidectomy	26%	35%
	Ear Tube	48%	49%
	Shunt	0%	0%
	Cervical fusion	4%	2%
	Hip Surgery	0%	0%
	Heart Valve	0%	2%

Table 2
ADL scores for age-matched controls, patients with attenuated phenotypes, and patients with severe phenotypes.

		Subject age range (years)				
		0-5	5-10	10-15	>15	
Control	n	46	54	25	13	
	Movement	14.96 ± 6.10	19.43 ± 0.57	19.96 ± 0.20	20	
	Movement Cognition	9.46 ± 6.71	19.38 ± 1.47	19.88 ± 0.44	20	
	Cognition	8.87 ± 4.63	16.07 ± 1.80	18.76 ± 1.37	20	
Severe	n	4	10	15	21	
	Movement	15.75 ± 2.22	15.25 ± 4.44	10.07 ± 5.11	7.31 ± 7.12	
	p ^a	NS	0.0155	9.01E-05	8.53E-08	
	Movement Cognition	6.5 ± 2.1	7.90 ± 2.83	5.79 ± 4.33	5.86 ± 6.05	
	p ^a	NS	8.27E-08	1.62E-08	9.88E-10	
	Cognition	4±2.45	4.4±2.11	2.93±2.95	3.21±3.20	
	p ^a	0.0128	3.58E-10	1.97E-13	3.07E-16	
Attenuated	n	-	4	8	13	
	Movement	-	17.67 ± 1.52	19.5 ± 0.76	18.73 ± 3.26	
	p ^a	-	NS	NS	0.0498	
	Movement Cognition	-	18.66 ± 1.15	19.5 ± 1.07	17.63 ± 5.62	
	p ^a	-	NS	NS	NS	
	Cognition	-	10 ± 1.73	19.25 ± 1.16	16.92 ± 5.89	
	p ^a	-	1.80E-02	NS	1.32E-03	
<i>t</i> -test between phenotypes						
Movement		-	NS	1.74E-05	2.20E-06	
Movement w/cognition		-	5.24E-06	6.89E-09	6.33E-06	
Cognition		-	9.54E-03	2.47E-13	3.88E-08	

^aStudent's *t*-test between phenotype and control; NS: no statistical significance at *p* < 0.05

Table 3

ADL scores for severe forms of patients treated by ERT and HSCT.

		Subject age range (years)				
		0-5	5-10	10-15	>15	
HSCT	n	1	6	4	7	
	Movement	17	17.58 ± 2.31	13.5 ± 7.04	13.71 ± 5.82	
	Movement Cognition	7	8.5 ± 5.59	7.25 ± 5.44	10.86 ± 3.29	
	Cognition	2	5.33 ± 1.37	3 ± 4.24	4 ± 3.29	
Early ERT (under 8 years)	n	3	3	9	1	
	Movement	15.33 ± 2.51	12.33 ± 2.31	10.33 ± 4.41	15	
	Movement Cognition	6.33 ± 2.52	6.66 ± 3.21	5.78 ± 3.77	8	
	Cognition	4.66 ± 2.52	2.66 ± 2.88	3 ± 2.40	6	
Late ERT (over 8 years)	n	-	-	2	11	
	Movement	-	-	3.5 ± 4.95	3.77 ± 4.84	
	Movement w/cognition	-	-	2 ± 2.83	3.36 ± 3.61	
	Cognition	-	-	2.5 ± 3.54	2.68 ± 3.35	
t-test between HSCT and early ERT	Movement	-	NS	NS	-	
	Movement w/cognition	-	NS	NS	-	
	Cognition	-	NS	NS	-	
t-test between HSCT and late ERT	Movement	-	-	-	0.03	
	Movement w/cognition	-	-	-	0.03	
	Cognition	-	-	-	NS	

NS: no statistical significance at p < 0.05; HSCT: hematopoietic stem cell transplantation; ERT: enzyme replacement therapy