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Authors
Lund, Troy C
Cathey, Sara S
Miller, Weston P
et al.

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Outcomes after Hematopoietic Stem Cell Transplant for Children with I-Cell Disease

Troy C. Lund, MSMS, PhD, MD, FAAP[1], **Sara S. Cathey, MD**[2], **Weston P. Miller, MD**[1], **Mary Eapen, MBBS, MS**[3], **Martin Andreansky, MD, PhD**[4], **Christopher C. Dvorak, MD**[5], **Jeffrey H. Davis, MD**[6], **Jignesh D. Dalal, MD**[7], **Steven M. Devine, MD**[8], **Gretchen M. Eames, MD, MPH**[9], **William S. Ferguson, MD**[10,11], **Roger H. Giller, MD**[12], **Wensheng He**[3], **Joanne Kurtzberg, MD**[13,14], **Robert Krance, MD**[15], **Emmanuel Katsanis, MD**[16], **Victor A. Lewis, MD**[17], **Indira Sahdev, MD**[18], and **Paul J. Orchard**[1]

[1]Division of Pediatric Blood and Marrow Transplant, University of Minnesota, Minneapolis, MN

[2]Greenwood Genetic Center, Greenwood, South Carolina

[3]Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

[4]Division of Pediatric Hematology/Oncology, University of Miami, Jackson Memorial Hospital, Miami, FL

[5]Department of Pediatrics, University of California San Francisco Medical Center, San Francisco, CA

[6]Department of Pediatrics/BMT Service, British Columbia's Children's Hospital, University of British Columbia, Vancouver, BC, Canada

[7]Department of BMT, The Children's Mercy Hospital and Clinics, Kansas City, MO

[8]Division of Hematology, James Cancer Center, Ohio State Medical Center, Columbus, OH

[9]Hematology and Oncology Center, Cook Children's Medical Center, Fort Worth, TX

[10]Department of Hematology/Oncology, Cardinal Glennon Children's Medical Center, St. Louis, MO

[11]St. Louis Cord Blood Bank, St. Louis, MO

[12]Section of Hematology, Oncology and BMT, Department of Pediatrics, Children's Hospital Colorado, University of Colorado, Aurora, CO

[13]Department of Pediatrics, Duke University Medical Center, Durham, NC

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Corresponding Author: Troy Lund MSMS PhD MD FAAP, Assistant Professor, University of Minnesota, Pediatric Blood and Marrow Transplant Program, Stem Cell Institute, Global Pediatrics, MMC 366, 420 Delaware St SE, Minneapolis, MN 55455, Phone: 612-625-4185, lundx072@umn.edu.

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[14]Pediatric Blood and Marrow Transplant Program, Carolinas Cord Blood Bank, Durham, NC

[15]Section of Hematology-Oncology, Department of Pediatrics, Baylor College of Medicine Center for Cell and Gene Therapy, Houston, TX

[16]Department of Pediatrics, University of Arizona Medical Center, Tucson, AZ

[17]Department of Hematology/Oncology/Transplant Program, Alberta Children's Hospital, Calgary, AB, Canada

[18]Division of Pediatric Hematology/Oncology/Stem Cell Transplantation, Cohen Children's Medical Center of New York, New Hyde Park, NY

Abstract

Mucolipidosis type II (MLII), or I-Cell Disease, is a rare, but severe disorder affecting localization of enzymes to the lysosome, generally resulting in death before the 10th birthday. Although hematopoietic stem cell transplant (HSCT) has been used to successfully treat some lysosomal storage diseases, there have been only two case reports in the use of HSCT to treat MLII. For the first time, we describe the combined international experience in the use of HSCT for MLII in 22 patients. Although 95% of the patients engrafted, the overall survival was low with only 6 patients (27%) alive at last follow-up. The most common cause of death post-transplant was cardiovascular complications, most likely due to disease progression. Survivors were globally delayed in development, and often required complex medical support such as gastrostomy tubes for nutrition, and tracheostomy with mechanical ventilation. Although HSCT has demonstrated efficacy in treating some lysosomal storage disorders, the neurologic outcome and survival for patents with MLII were poor. Therefore new medical and cellular therapies should be sought for these patients.

Introduction

Mucolipidosis type II (MLII), or I-cell Disease, is a rare autosomal recessive disorder caused by mutation in the *GNPTAB* gene on chromosome 12. This gene encodes the α/β subunits of the enzyme N-acetylglucosamine-1-phosphotransferase (GNPT) which acts to couple phosphate groups to mannose residues (mannose-6-phosphate moieties, M6P) on enzymes destined to be targeted to the lysosome. Mutation in *GNPTAB*, with resultant abnormal GNPT function, can lead to inappropriate trafficking of lysosomal enzyme to the extracellular compartment. Pathologically, dense and dark granules, visible on phase-contrast microscopy, fill the cytoplasm of cultured fibroblasts, so-called inclusion cells, or I-cells. A complete absence of GNPT activity results in the severe storage disease, MLII, characteristically evident in infancy or even prenatally.

Clinical findings include coarse facial features, dysostosis multiplex, growth failure, global development delay, generalized hypotonia but stiff joints, and recurrent respiratory infections progressive. Death often occurs in the first decade of life from cardio-pulmonary disease[1-3]. For patients with lysosomal storage disorders, HSCT aims to provide donor-derived hematopoietic cells that produce lysosomal enzymes with M6P moiety allowing for intracellular uptake with appropriate trafficking to the lysosomal for substrate degradation. This “cross-correction” provided by transplanted cells has been used successfully for

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treatment of several enzyme-specific lysosomal storage disorders notably mucopolysaccharidosis type I, Gaucher disease, and alpha-mannodidosis[4-11]. However, in the case of I-cell Disease, the gene product is not a soluble enzyme capable of internalization through binding to M6P receptors on the cell surface. The use of HSCT to treat I-cell Disease has not been previously reported beyond two case reports [12,13]. We now describe the largest collection of outcome data on 22 patients with I-cell Disease who underwent HSCT.

Methods

Data Collection

Patient-, disease- and transplant-related data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a voluntary working group of more than 450 transplantation centers that contribute detailed data on consecutive allogeneic and autologous transplantations to a Statistical Center at the Medical College of Wisconsin in Milwaukee or the National Marrow Donor Program in Minneapolis. Participating centers are required to report all transplants consecutively and compliance is monitored by on-site audits. Patients are followed longitudinally until death or until they are lost to follow-up. All patients provided written informed consent for data submission and research participation. The study was approved by the Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program.

Inclusion criteria

Patients were identified by query of the CIBMTR database for the diagnoses “mucolipidosis, type II” or “I-cell Disease.” Records were reviewed to verify the molecular or enzyme-based diagnosis. All patients undergoing first or second allogeneic HSCT for MLII were considered.

Outcomes

The primary endpoint was overall survival (OS). Other outcomes studied include time to neutrophil engraftment (defined as the first day achieving an absolute neutrophil count ≥0.5 × 10^9/L for three consecutive measurements), platelet engraftment (defined as the first day when platelets remained ≥ 20 × 10^9/L without transfusions for 7 days), incidence of acute graft-versus-host disease (GvHD), and chronic GvHD. Acute and chronic GVHD were defined using standard criteria [14,15].

Results

Patient and Graft Characteristics

We identified 22 patients reported to the CIBMTR who underwent allogeneic HSCT for MLII or I-cell disease (summarized in Table 1). Patients were transplanted at a median age of 9 months (range 2 – 23 months) and at a median of 3 months after diagnosis (range 2 – 20 months). There were 12 females and 10 males in this cohort with the majority having Lansky performance scores of 80 or higher at transplantation. Cell sources varied with 14 patients receiving unrelated umbilical cord blood (UCB) with the majority of these being 5/6

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or 6/6 HLA-matched to the recipient. Of the remaining 8 patients, 3 patients received HLA-matched sibling bone marrow (carrier status was unknown), one patient received bone marrow from the mother, another received bone marrow from the father, and three patients received bone marrow from unrelated adult donors (n=1 HLA-matched; n=2 HLA-mismatched).

Preparative regimens varied. Most were busulfan–based and myeloablative in intent, though five patients received a reduced intensity regimen. GVHD prophylaxis consisted largely of cyclosporine (CSA) and steroids, though other regimens were also employed.

Thirteen of 22 patients had documented DNA mutation analysis confirming the diagnosis of MLII. Interestingly, three patients (patients 4, 9, and 17) were found to have a genotype consistent with the less severe Intermediate MLII/MLIII. It has been reported that these affected patients have mutations in the same *GNPTAB* gene as MLII, though retain some GNTP activity and have a milder phenotype[16]. However, one of these three died of organ failure more than 2 years following transplant, which suggests that mortality in this case resulted from underlying disease. On the other hand, one of these also died of pneumonitis shortly after transplant, a complication that was likely due to the transplant procedure itself.

Outcomes

Primary engraftment was obtained in 19/22 patients with a median time to neutrophil and platelet engraftment of 17 days and 37.5 days respectively. Engraftment status was not known in two patients; however both died within 6 months. One patient had early secondary graft failure defined as sustained loss of neutrophil recovery in the absence of infection. This patient (patient#6) received a second transplant within two months from the first transplant and a third transplant 15 months after the second transplant. The donor source was adult unrelated donor. This patient is alive, approximately 10 years from first transplantation. Another patient (patient#9) developed a post-transplant lymphoma (PTL) in the liver and was treated with surgical resection and two infusions (one month apart) of sibling donor lymphocytes at 10.5 and 11.5 months post-transplant with resolution of her PTL. Five of the six survivors listed in Table 1 had 100% donor chimerism at 1 – 2 years post HSCT (no chimerism data was available for patient#21).

Grade 1 - 2 acute GvHD was documented in nine patients. Grade 3 aGVHD was seen in only one patient. There were three patients with documented chronic GVHD, and both had been previously diagnosed with Grade 2 aGVHD. The probability of 5-year overall survival was 33% (95% CI 15 - 55) with a median follow-up 67 months (Figure 1); 27% of patients (n=6) were alive at last contact. The median time to death was 27.6 months. The most common cause of death given was “organ failure” (6 patients) followed by primary disease progression (3 patients) and interstitial pneumonia (3 patients).

While numerous reports have provided increasing amounts of information regarding survival and transplant related outcomes for lysosomal storage disorders, the prevalence and severity of developmental delays associated with these disorders has been more difficult to measure. Consistent neuropsychiatric measures that are used across multiple centers would be ideal in these assessments, but were not available in this cohort of patients. We attempted

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a basic functional evaluation by sending a simple questionnaire to transplant centers to inquire as to the status of surviving patients and received information on six patients, one of whom had genetic testing indicating an Intermediate form of MLII/MLIII (Table 2). There was significant morbidity in these post-transplant MLII patients that was likely related to their underlying disease, as they were described as requiring gastrostomy tubes for nutrition, ventilatory support per a tracheostomy, having an impaired ability to ambulate, and being very delayed in speech and learning. Though this data is far from comprehensive, it documents that a high degree of medical support was required for children with MLII post-transplant, and that much of this support appears to be related to the underlying disease rather than the transplant procedure.

Discussion

We have described the largest series of patients undergoing HSCT for Mucolipidosis type II, or I-cell Disease. HSCT has been used for the metabolic “cross-correction” of lysosomal storage diseases for over 30 years, with the majority of patients having severe mucopolysaccharidosis type I (MPSI-H). From these patients we have learned that HSCT can arrest the fatal neurodegeneration of MPSI-H allowing patients to live significantly longer with improved function and quality of life. Patients undergoing HSCT for MPSI-H earlier in life (ideally prior to age 2 years) have been shown to lose less developmental ground and perform better. However, while HSCT may help alleviate visceral and neurological disease associated with MPSI-H, its impact on orthopedic and cardiac valve pathology may be limited [8,17-19].

The overall survival at last follow-up in our cohort is strikingly low at 27%, with the median time to death of 27.6 months. This suggests that these fatalities were not due to peri-transplant related toxicity, but due to disease related complications that were not alleviated with transplantation. Specifically, although several reported causes of death were listed as “organ failure,” as these occurred later after transplant, we presume that some of these were due to progressive disease. Because MLII is rare, its natural history is documented mainly as case reports or small case series. These reports suggest that most patients do not survive past the first decade and die from cardio-respiratory complications [3,20]. Although our data show that there are two patients post-transplant over the age of 10 (patients 6 and 9), patient 9 (who has the longest follow-up) was later determined to have an intermediate form of MLII/MLIII on review of her mutation. Interestingly, patient 9 was one of the first case reports of HSCT for I-Cell Disease[12].

The correlation of phenotype to genotype has only recently been reported by Cathey *et al.* who described, for the first time, 61 patients with mutations in *GNPTAB* and found that some mutations fell into clinical separations of MLII (I-Cell), MLIII, and an intermediate form of MLII/MLIII. On this basis, we cannot conclude that HSCT favorably changed the clinical outcome for this patient, as her survival and neurologic status are not clearly different than that of an Intermediate MLII/III patient. In comparison to classic MLII, Intermediate MLII/III patients tend to be taller, develop complications at a later age, have less pronounced skeletal issues, less severe neurocognitive deficits, and a greater life span[16]. Furthermore, upon evaluation of the available molecular mutations for patients in this

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cohort, three patients had mutations consistent with a milder phenotype than the classical MLII (Table 1).

Our limited neurologic follow-up showed that after transplant, many of the children are still severely affected by their disease, requiring significant medical interventions. It is unclear if they displayed any “true” improvement in neurological development. HSCT has been attempted for several lysosomal storage diseases, though not all diseases are improved after HSCT. Also, HSCT outcomes are generally poor for patients who are in an advanced neurologic decline prior to transplant. We can speculate on several reasons for poor outcome after HSCT. It is believed that delivery of lysosomal enzymes by donor-derived hematopoietic cells requires the 6-mannose phosphate moiety to allow targeting to the lysosome. In the case of MLII, disruption of the pathway by which the M6P signal is associated with the enzyme affects not just one enzyme, but numerous enzymes. This results in inappropriate secretion and insufficient delivery of multiple enzymes to the lysosome. The result is the accumulation of macromolecular substrates that create inclusions in cells (giving rise to the namesake I-Cells), ultimately, making MLII a very severe form of lysosomal storage disease due to insufficient activity of most of the lysosomal enzymes. Evaluation of lysosomal enzyme activity in MPSI patients can show correction toward normal after HSCT, but in MLII patients, the inappropriate plasma secretion of several enzymes (ß-galactosidase, ß-hexosaminidase A, α-mannosidase, ß-mannosidase, ß-glucoronidase, α-glucosaminidase, α-L-fucosidase) remains significantly elevated months to years after successful HSCT (personal observation). One could speculate that this represents an incomplete lysosomal correction of disease by HSCT insufficient to prevent continued pathologic consequences.

In conclusion, we have little to no evidence that HSCT leads to improved clinical/ neurological outcomes in MLII. Overall patient survival is poor, as is quality of life among those who do survive. New modifications to HSCT or complementary therapies such as gene therapy, enzyme replacement, or substrate reduction are needed to improve outcomes in this population of children.

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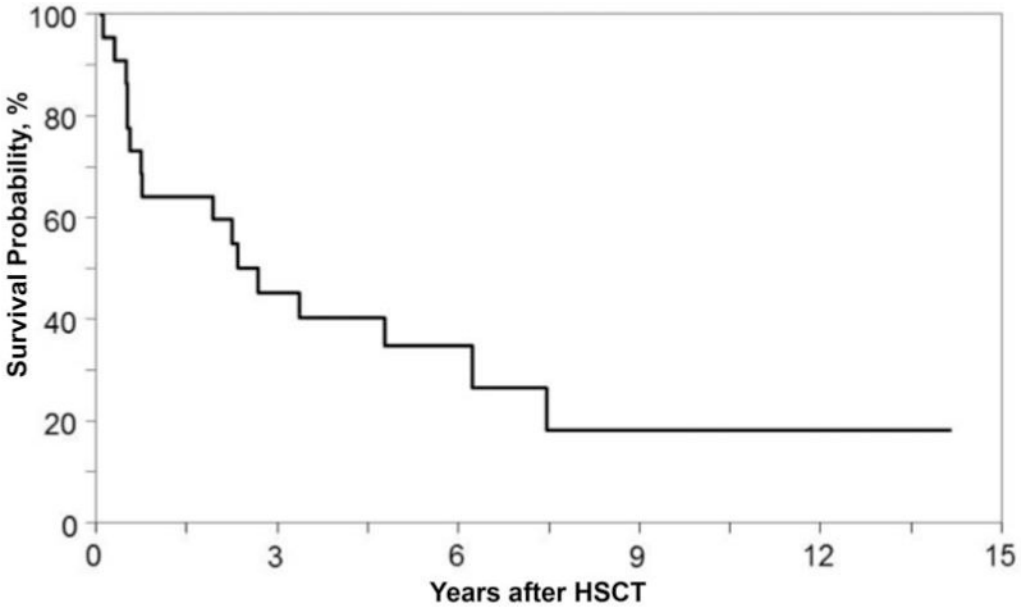

Figure 1.
Kaplan-Meier estimate of overall survival in I-Cell patients after transplant.

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Table 1

Patient and Transplant Characteristics. Performance scores are given as Lansky scores. Chemotherapy regimens consisted of anti-thymoglobulin (ATG), busulfan (Bu), cytoxan (Cy), melphalan (Mel), fludarabine (Flu) and the conditioning intent classified as either myeloablative (MAC) or reduced intensity conditioning (RIC). Graft versus host prophylaxis: cyclosporin (CSA), mycophenolate mofetil (MMF), methotrexate (MTX). Data which was not available is listed as n/a.

Patient ID	Year of Transplant	Time from Dx to Transplant (months)	Age at transplant (months)	Sex	Performance score at transplant	HLA-Match and Graft Source	Conditioning regimen	GVHD prophylaxis	aGVHD grade Gluksberg	cGVHD	HSCT to last contat (months)	Status	Cause of death	*GNTPAB* Mutation
1	2005	n/a	9	Female	100	5/6 UCB	ATG, Bu, Cy (MAC)	Seroids + CSA	2	No	8.5	Dead	Organ Failure	Diagnosed by enzyme testing, no molecualr data.
2	2006	n/a	4	Male	100	6/8 unrelated BM	ATG, Bu, Cy (MAC)	ATG, CSA, MTX	3	No	54.1	**Alive**		Diagnosed by enzyme testing, no molecualr data.
3	2007	n/a	13	Male	90	5/6 UCB	Mel, Clof, 200 cGyTBI (RIC)	CSA, MMF	0	No	62	**Alive**		Frameshift detected, second mutation not detected by standard sequencing.
4	2000	n/a	14	Male	90	4/8 unrelated BM	Bu, Cy (MAC)	TCD, ATG, Seroids, CSA	0	No	27.6	Dead	Organ Failure	Frameshift + missense mutations giving a diagnosis of either intermediate MLII or ML III.
5	2002	n/a	4	Female	70	6/6 UCB	ATG, Bu, Cy (MAC)	Steroids, CSA	2	Yes	5.5	Dead	Interstitial pnueumonia	Diagnosed by enzyme testing, no molecualr data.
6	2002	n/a	13	Male	60	6/6 unrelated BM	Campath, Flu (RIC)	Tacrolimus	2	Yes	117.4	**Alive**		Diagnosed by enzyme testing, no molecualr data.
7	2007		19	Female	100	6/6 UCB	ATG, Bu, Cy (MAC)	Tacrolimus, MMF	0	No	62.8	**Alive**		Compound heterozygous frameshift mutation + nonsense muation.
8	1999	3	4	Male	n/a	HLA match unknown UCB	ATG, Bu, Mel (MAC)	Steroids, CSA	n/a		6.1	Dead	Organ Failure	Diagnosed by enzyme testing, no molecualr data.
9	1997	20	20	Female	80	Sibling BM	Bu, Cy, 750 cGy TBI (MAC)	TCD	2	No	171.1	**Alive**		Frameshift + a splice change givng a milder than expected phenotype, intermediate MLII/MLIII.
10	2000	2	4	Male	>=80	5/6 related BM from Mother	ATG, Bu, Cy (MAC)	Steroids, CSA	0	No	40.1	Dead	Primary Disease	Compound heterozygous frameshift mutations.
11	2004	3	23	Female	n/a	6/6 UCB	ATG, Bu, Cy (MAC)	Steroids, CSA	0	n/a	98	Dead	Unknown	Compound heterozygous frameshift mutation + nonsense muation.
12	2005	3	6	Female	>=80	5/6 UCB	ATG, Cy (RIC)	CSA, MMF	2	No	57.2	Dead	Infection	Compound heterozygous frameshift mutation + nonsense muation.
13	2005	5	18	Female	>=80	6/6 UCB	ATG, Cy (RIC)	CSA, MMF	0	No	90	Dead	Primary Disease	Homozygous frameshift mutation.
14	1991	n/a	n/a	Male	n/a	Other related BM	Cy, TBI (MAC)	CSA	n/a	n/a	2.9	Dead	Unknown	Diagnosed by enzyme testing, no molecualr data.

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Patient ID	Year of Transplant	Time from Dx to Transplant (months)	Age at transplant (months)	Sex	Performance score at transplant	HLA-Match and Graft Source	Conditioning regimen	GVHD prophylaxis	aGVHD grade Gluksberg	cGVHD	HSCT to last contat (months)	Status	Cause of death	*GNTPAB* Mutation
15	1996	2	9	Male	90	Silbling BM	ATG, Bu, Cy (MAC)	CSA, MTX	1	No	31.7	Dead	Interstitial Pnueumonia	Diagnosed by enzyme testing, no molecualr data.
16	2008	3	15	Male	90	5/6 UCB	ATG, Bu, Cy (MAC)	CSA, MMF	2	Yes	22.7	Dead	Organ failure	Frameshift + a splice change giving a milder than expected phenotype, intermediate MLII/MLIII.
17	2008	10	10	Female	100	5/6 UCB	Campath, Bu, Cy (MAC)	Tacrolimus, MTX	0	No	0.6	Dead	Interstitial pnueumonia	Diagnosed by enzyme testing, no molecualr data.
18	2008	8	8	Female	n/a	5/6 UCB	ATG, Bu, Flu (MAC)	Steroids, CSA	2	No	5.3	Dead	Organ failure	Compound heterozygous frameshift mutation + nonsense muation.
19	2010	3	3	Female	100	6/6 UCB	Campath, Mel, Clof, 200 cGy TBI (RIC)	CSA, MMF	0	No	8.3	Dead	Primary Disease	Homozygous nonsense mutation.
20	2010	2	2	Female	100	Sibling BM	ATG, Bu, Flu (MAC)	CSA	0	No	5.4	Dead	Organ Failure	Compound heterozygous frameshift mutation + nonsense muation.
21	2010	10	10	Male	100	5/6 UCB	ATG, Bu, Cy (MAC)	Steroids, CSA	2	No	89	**Alive**		No repsonse from center.
22	2011	5	5	Female	90	4/6 UCB	ATG, Bu, Cy (MAC)	Steroids, CSA	0	No	26	Dead	Pulmonary Failure	Homozygous frameshift mutation.

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Table 2

Summary of results of questionnaire to assess neurologic status in MLII patients after transplantation. Patient 9 had a molecular diagnosis consistent with Intermediate MLII/III. Two patients died soon after the assessment was taken.

Patient ID	Gastrostomy tube	Tracheostomy	Wheelchair use	Can they walk?	Speech?	Chronologic age	In School?	Pottytrainied	Status
3	yes	yes	yes	never	no	7 years	functions at a 6-9 month old level	no	Alive
7	yes	yes	yes			8 years	never in school, homebound teacher 1 day per week		Alive
9	no	no	sometimes	yes	some	18 years	functions at a 4 year old level	yes	Alive
13	yes	yes	yes	never	no	9 years	no	no	Died
21	yes	yes	no	no, and no wheelchair		4 years	no		Alive
22	yes	no	custom wheelchair	never walked	no	2.5 years	never achieved age for education	no	Dead