SCIENTIFIC ARTICLE

The Frequency of Carpal Tunnel Syndrome in Hurler Syndrome After Peritransplant Enzyme Replacement Therapy: A Retrospective Comparison

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Purpose Children with Hurler syndrome (HS) develop carpal tunnel syndrome (CTS) owing to glycosaminoglycan deposition secondary to enzyme deficiency. Advancement in the treatment of the underlying enzyme deficiency now commonly includes peritransplant intravenous enzyme replacement therapy (ERT). The primary objective of this study was to determine if the use of limited ERT in addition to hematopoietic stem cell transplantation (HCT) for the treatment of children with HS reduces the incidence of surgical intervention for CTS compared with a cohort of historical controls treated with HCT alone. The secondary objectives were to evaluate the impact of demographic and transplant-related characteristics on the incidence of CTS. Lastly, the results of surgical treatment of CTS in HS are reported.

Methods Medical records for a historical group of 43 HS patients who underwent HCT alone (group 1) were compared with 31 HS patients who underwent HCT + ERT (group 2). Both groups were compared for genotype, age at transplant, sex, transplant graft source, median/ulnar nerve conduction study parameters as well as the incidence and treatment of CTS. Pre- and postoperative nerve conduction studies were compared for children treated surgically for CTS.

Results The cumulative incidence of CTS at 5 years for HS children treated with HCT + ERT was 51% compared with 47% for HS children treated with HCT alone. The incidence of CTS did not depend upon graft source, age at transplant, or sex. Median nerve conduction velocity for both sensory and motor potentials demonstrated significant improvement after carpal tunnel release.

Conclusions Although the administration of ERT prior to and for several months after HCT has become routine in our institution, our findings do not suggest this combined therapy is sufficient to decrease the development of CTS. Surgical intervention for median nerve compression remains the treatment of choice for CTS in HS children. *(J Hand Surg Am. 2017;42(7):573.e1-e8. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic IV.

Key words Pediatric carpal tunnel, carpal tunnel syndrome, Hurler syndrome, mucopolysaccharidosis, enzyme replacement therapy.

Online Exclusive

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HURLER SYNDROME (HS) IS A RARE autosomal recessive disorder caused by severe mutations in the gene encoding alpha-L-iduronidase (*IDUA*) enzyme and is one of the mucopolysaccharide storage disorders. With a deficiency in *IDUA*, the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate are not degraded, with resulting accumulation affecting multiple organ systems. The accumulation of GAGs leads to decreased tissue compliance and added bulk. Accumulation occurs in the musculoskeletal system with manifestations including thoracolumbar kyphosis, hip dysplasia, genu valgum, and carpal tunnel syndrome (CTS), among others.[1–3]

For HS children, the risk for development of CTS has historically been shown to be high, occurring early in life for up to 73% of untreated patients.[4–6] The pathophysiology of CTS is multifactorial and includes GAG accumulation within the carpal bones leading to diminished size of the carpal tunnel, accumulation within flexor tendon tenosynovium leading to increased contents within the carpal tunnel, and probable deposition within the median nerve itself leading to impaired nerve function. The classic symptoms of adult CTS (pain, dysesthesias) are often not present in pediatric HS patients. With the slow onset of deposition, the possibility of impaired cognition, and young age at presentation, presenting complaints can include "clumsiness," rubbing or shaking of digits, avoidance of thumb prehension, reversion to ulnar raking grasp, self-mutilation via chewing on radial digits, waking owing to hand complaints, or sometimes no complaint at all, thus making the clinical diagnosis of CTS in HS patients difficult. Because of the inconsistency of presenting signs and symptoms for CTS in HS children, screening for CTS with nerve conduction velocity (NCV) studies or referral to a hand specialist is imperative for diagnosis.

Hematopoietic stem cell transplantation (HCT) has been shown to increase life expectancy in HS by improving the natural history of fatal neurological and cardiac symptoms but has not altered the development of orthopedic manifestations.[7–9] In 2003, the approval of intravenous (IV) *IDUA* laronidase as enzyme replacement therapy (ERT) made it possible to use laronidase in association with HCT, with the goal of decreasing the GAG burden prior to transplant.[10] Although IV laronidase does not cross the blood-brain barrier, it has been shown to decrease the somatic accumulation of dermatan and heparan sulfate.[11,12] Recent reports have demonstrated a high rate of engrafted survival using this tandem approach, utilizing enzyme prior to transplant and for a limited time after transplant.[13]

The addition of peritransplant ERT to the routine treatment of HS has not been studied with respect to its effect on later development of CTS. The hypothesis of this study was that the incidence of CTS is lower in HS children treated with HCT + ERT (group 2) compared with a historical cohort undergoing HCT alone (group 1). As secondary outcomes, the effect of age at transplant, graft type, and sex on the incidence of CTS are reported. Lastly, this study provides nerve conduction study (NCS) data before and after surgical intervention of CTS in HS children.

METHODS

Inclusion criteria

Medical records from 2 participating academic hospitals in Minnesota were reviewed for patients with a diagnosis of HS during the study period 1985 to 2012. Inclusion criteria were (1) a diagnosis of mucopolysaccharidosis type 1H (HS); (2) treated with HCT (group 1) or HCT + ERT (group 2) with at least 1 year survival; and (3) evaluation by hand surgery (A.V.H.) including NCS testing (Fig. 1). At our center, a close referral relationship exists among all areas of care for patients affected with HS, including pediatrics, oncology, endocrinology, neurology, psychiatry, and orthopedics as well as physical and occupational therapy. Clinical visits are bundled to facilitate patient compliance and coordination. Between the ages of 2 and 5 years, all transplanted patients are evaluated by a hand surgeon along with a screening NCS. Demographics, transplant characteristics, and NCV testing results were recorded for all patients. If patients underwent more than 1 transplant attempt, the latter was used as the time of transplantation. One patient transplant occurred at an alternate institution.

Demographics and transplant characteristics

Eighty-three patients were identified with the diagnosis of HS and who underwent HCT during the study period. Excluded from analysis were 8 patients not surviving 1 year after HCT, and 1 patient who was never evaluated by hand surgery. Forty-three patients met the inclusion criteria for group 1 and 31 met inclusion criteria for Group 2. As shown in Table 1, sex distribution was similar in groups 1 and 2. Median age at HCT was 1.7 years for group 1 and 1.4 years for group 2, ranges 0.5 to 6 years and 0.6 to 2.9 years, respectively. Mean follow-up is 5 years for

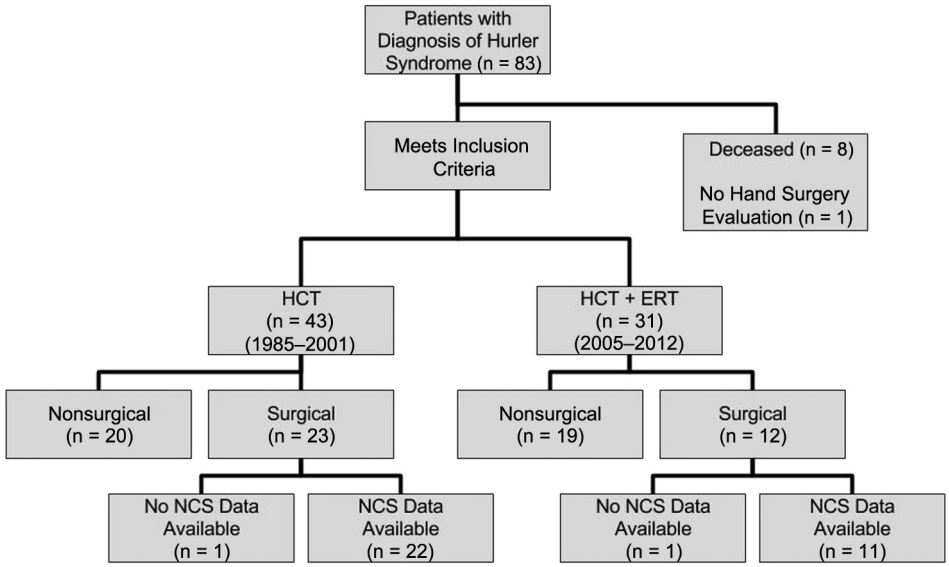

FIGURE 1: Flow diagram represents the groups included (inclusion/exclusion criteria).

TABLE 1. Demographic and Transplant Characteristics

Characteristic	Group 1: HCT	Group 2: HCT + ERT
n	43	31
Age at HCT (y), mean (range)	1.8 (0.5–6.0)	1.5 (0.4–2.9)
Male, n (%)	24 (56)	17 (55)
Related marrow donor, n (%)	19 (44)	6 (19)
Unrelated marrow donor, n (%)	19 (44)	2 (6)
Umbilical cord blood, n (%)	5 (12)	23 (74)
4/6 HLA match, n (%)	1 (2)	1 (3)
5/6 HLA match, n (%)	9 (21)	10 (32)
6/6 HLA match, n (%)	30 (70)	19 (61)
Unknown, n (%)	3 (7)	1 (3)
Full engraftment, n (%)	32 (74)	21 (68)
Partial engraftment, n (%)	9 (21)	7 (23)
Failed engraftment, n (%)	2 (5)	2 (6)
Unknown, n (%)	0 (0)	1 (3)
Genotype data available, n	20	19
Null/null genotype (common non-sense alleles Q70X, W402X)	12/20	11/19
Null/+ or +/+	8/20	7/19

HLA, human leukocyte antigen.

group 2 and 15 years for group 1, in that group 1 was a historical control.

Patients transplanted prior to 2003 were treated with HCT alone (group 1). Patients transplanted from 2003 to 2012 received peritransplant laronidase ERT, hereafter HCT + ERT (group 2). Conditioning regimens and graft selection for transplant were per existing institutional protocols and guidelines. Peritransplant laronidase was administered intravenously at a dose of 0.58 mg/kg weekly. Patients in group 2 generally received 12 laronidase doses pretransplant and 8 doses following transplant, although the actual total doses varied based on the clinical situation. In group 2, the mean number of laronidase doses received was 22 (median, 14; range, 10–88).

Transplant graft source (related donor, unrelated donor, or unrelated umbilical cord blood) was collected on all subjects. Data regarding carrier status of the related donor grafts were not available. Human leukocyte antigen match characteristics between the graft and the recipients were recorded. Posttransplant hematopoietic engraftment (chimerism) was classified according to percentage donor contribution: full (99%−100%), partial (50%−98%), or failed (0%−49%). The HS genotype of all subjects was recorded where available and *IDUA* mutations were classified as non-sense (such as the common null alleles Q70X and W402X) or mis-sense. Patients were then stratified into biallelic non-sense (null/null), mis-sense (+/+) or mixed (null/+) genotype.

Institutional review board statement

This study was approved by the institutional review board, and informed consent was obtained from each patient as part of a larger database collection.

Nerve conduction studies

Classic symptoms of CTS such as median nerve paresthesia, pain, and thenar atrophy are infrequently present in HS patients owing to their young age (2−5 years old) and impaired mentation. The diagnosis is based on NCSs. Nerve conduction velocity of the ulnar nerve across the wrist over the same distance and at the same temperature as the conduction velocity of the median nerve across the wrist were compared because normative data are not available for carpal tunnel assessment in young children. Sensory and motor latencies across the wrist were similarly compared for the ulnar and median nerves. Group 1 and group 2 were compared for all values: motor and sensory, right and left, median nerve and ulnar nerve. A positive study for CTS would typically be concluded if the median/ulnar peak latency (sensory or motor) constituted a 200% increase, or the corresponding median/ulnar conduction velocity was slowed to 70% or less, as correlated to their clinical findings by the hand specialist.

Thirty-five children were diagnosed with CTS based on these NCV criteria, 23 in group 1 and 12 in group 2. Nerve conduction studies were performed on all patients included; 3 patient studies were not available in our medical record but were documented in the clinical notes as negative examinations. Data were recorded for pre- and post-CTS surgery for conduction velocity and latency values of the median and ulnar nerves. Nerve conduction studies were performed for all patients diagnosed with CTS and quantitative data were available in the charts for 34 of the 35 preoperative cases. At 1 year or more before surgery, an NCS was performed for 25 of 35 patients. Most commonly, NCSs were performed when general anesthesia was indicated for procedures unrelated to CTS.

Statistical analysis

Because mean follow-up was 5 years for group 2 and 15 years for group 1, the frequency of CTS was normalized by comparing those who underwent surgery within 5 years of HCT.

The cumulative incidence function and two-sided log-rank test were used to evaluate time from HCT to CTS surgery. Two-sided unequal variance t-tests were used to compare NCS measurements between Groups and from pre- to post-surgical state.

Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) guidelines were used in the preparation of the study description.[14]

RESULTS

Primary objective

The cumulative incidence of CTS treated with carpal tunnel release at 5 years following HCT only was 47% (95% CI, 33−63). The cumulative incidence of CTS at 5 years following ERT + HCT was 51% (95% CI, 30−76) as shown in Figure 2 and Table 2.

Secondary objectives

Demographic and transplant characteristics were compared for groups 1 and 2 relative to the incidence of developing CTS. As shown in Figure 3, no difference was established for a delay in HCT until after the age of 2 years (5-year CTS incidence for age < 2 years was 48% [95% CI, 32−62], for age > 2 years 47% [95% CI, 21−68]). As shown in Figure 4, 5-year CTS incidence for females was 34% (95% CI, 17−52) and for males 58% (95% CI 39−73). As shown in Figure 5, 5-year CTS incidence with a related donor was 60% (95% CI, 38−77), umbilical cord blood 32% (95% CI, 12−53), and unrelated donor 46% (95% CI, 22−67).

Treatment of CTS

Thirty-five children were diagnosed with CTS and treated with open release of the transverse carpal ligament as well as debulking of the contents of the carpal tunnel with tenosynovectomy of the finger flexor tendons. At our institution, tenosynovectomy is performed routinely but has not been proven to change outcomes. Findings at the time of surgery included variable severity of narrowing of the median nerve (hourglass deformity) within the carpal tunnel

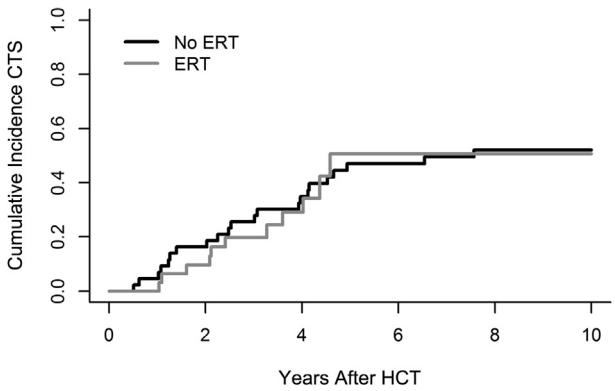

FIGURE 2: Cumulative incidence of developing CTS after HCT.

TABLE 2. Number of Hurler Children Who Developed CTS at 5 Years' Status After HCT With and Without the Use of ERT

Outcome	HCT	HCT + ERT	*P* Value
5-y CTS	47%	51%	.84
95% CI	33%, 63%	30%, 76%	
Mean age at surgery (y)	5.3	4.8	

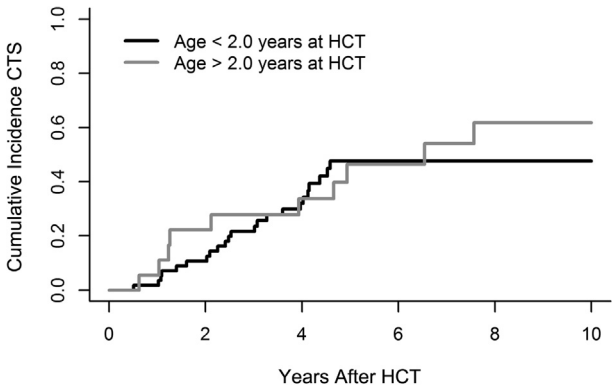

FIGURE 3: Cumulative incidence of CTS comparing age at transplant greater than 2 years.

(Fig. 6A),[15] as well as substantial tenosynovial deposits around the flexor tendons (Fig. 6B). The mean age at surgery for the entire group was 5.2 years, 5.3 years for group 1 and 4.8 years for group 2.

As shown in Table 3, the median nerve sensory and motor latencies were substantially prolonged compared with the ulnar nerve sensory and motor latencies prior to the surgery. Similarly, the median nerve sensory and motor conduction velocities were substantially slower compared with the ulnar nerve sensory and motor conduction velocities. This demonstrates that, whereas conduction through the carpal tunnel is diminished for most HS patients, additional

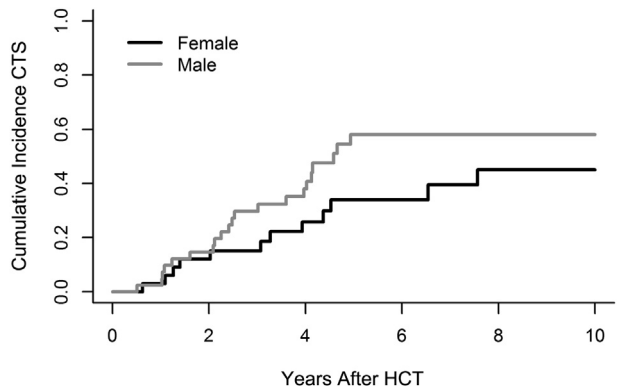

FIGURE 4: Cumulative incidence of CTS comparing male with female.

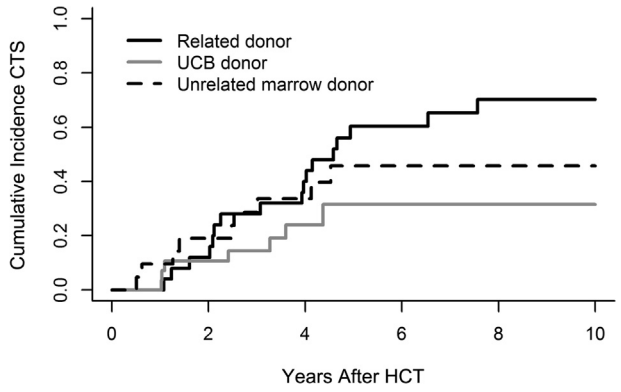

FIGURE 5: Cumulative incidence of CTS for donor type. UCB, umbilical cord blood.

treatment with ERT did not significantly protect against this characteristic difference when using the ulnar nerve conduction to normalize the values.

After carpal tunnel release, the mean difference between median and ulnar conduction latency (Fig. 7A) and velocity (Fig. 7B) showed improvement for all variables. When groups 1 and 2 are combined, the median NCV and motor latency demonstrated statistically significant improvement ($P < .05$) for all tests that had 10 or more patients as shown in Table 4.

DISCUSSION

The results of this study do not support the hypothesis that the incidence of CTS is lower in HS children treated with HCT + ERT (group 2) compared with a historical control cohort undergoing HCT alone (group 1). In our analysis, the strategy of limited use of ERT with HCT does not appear sufficient to affect the ultimate need for surgical correction of CTS associated with the disease. For patients with HS, peritransplant ERT has become routine practice in

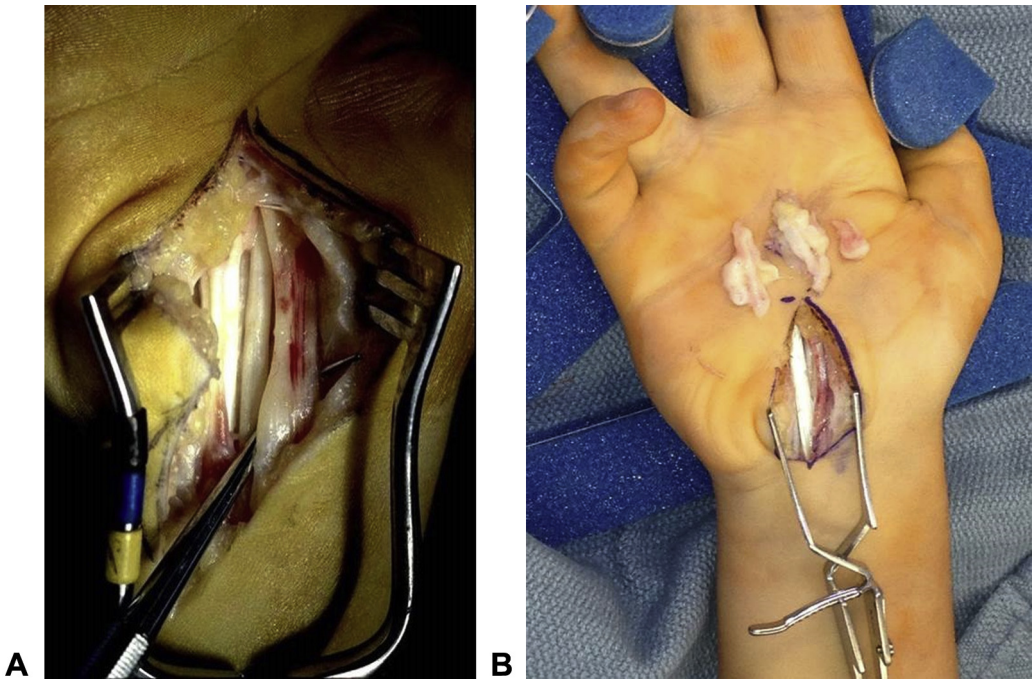

FIGURE 6: **A** Intraoperative photograph shows typical hourglass deformity present in the median nerve (overlying probe) at the time of transverse carpal ligament release. **B** Example intraoperative photograph after carpal tunnel decompression demonstrates the hypertrophic tenosynovial tissue typical of a patient with Hurler syndrome.

TABLE 3. Nerve Conduction Study Data for Groups 1 and 2 Before Surgery

Parameter	Group 1: HCT	Group 2: HCT + ERT	Δ Group 1 − Group 2 (95% CI)	*P* Value
Motor conduction velocity (m/s)				
Median	46.5	47.2		
Ulnar	54.1	58.2		
Δ Median − Ulnar	−7.6	−11.1	3.4 (−9.6, 16.5)	.58
Motor latency (m/s)				
Median	4.4	3.7		
Ulnar	1.9	1.9		
Δ Median − Ulnar	2.5	1.8	0.7 (−0.5, 1.9)	.25
Sensory conduction velocity (m/s)				
Median	38.3	43.2		
Ulnar	58.7	53.1		
Δ Median − Ulnar	−20.4	−9.9	−10.5 (−21.4, 0.3)	.06
Sensory latency (m/s)				
Median	3.0	2.7		
Ulnar	1.5	1.9		
Δ Median − Ulnar	1.5	0.8	0.6 (−0.2, 1.4)	.13

many centers and has been reported to result in excellent rates of engrafted survival in the modern era[2,13,16] but was not shown to change the incidence of CTS in this study.

It has previously been reported that, for each year older that a child is at the time of HCT, the incidence of CTS increases by 55%.[3] However, in the current study, patients younger than 2 years old at transplant had the same incidence of carpal tunnel surgery as patients older than 2 years. It has also been shown that the use of ERT can increase upper extremity joint range of motion, suggesting a reduced tissue burden

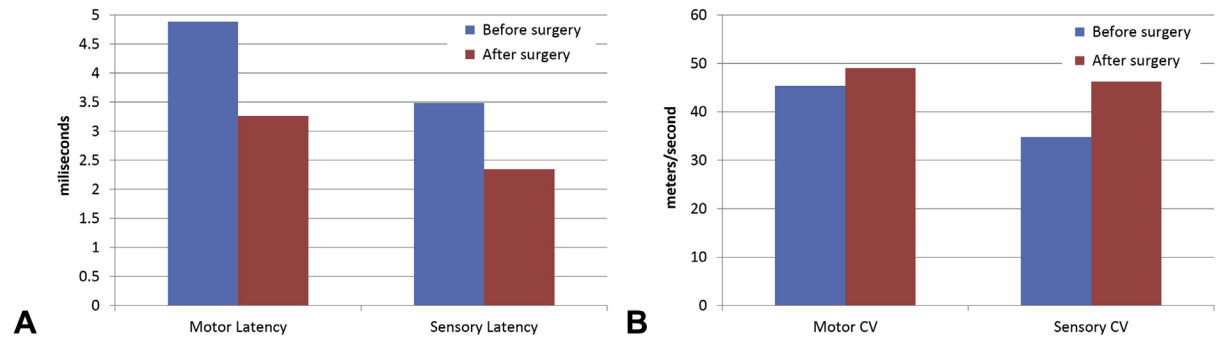

FIGURE 7: **A** Bar graph illustrates median nerve pre- and postsurgery average wrist latency for all patients who underwent surgical intervention. **B** Bar graph illustrates median nerve wrist conduction velocity (CV) for all patients who underwent surgical intervention.

TABLE 4. Comparison of Pre- and Post-Surgery Nerve Conduction Data for All Patients Who Underwent Surgical Intervention

	Mean Change	Lower 95% CI	Upper 95% CI	*P* Value	n
Median sensory latency (m/s)					
Right	−1.6	−2.2	−0.9	< .01	19
Left	−1.3	−1.7	−0.7	< .01	17
Median sensory conduction velocity (m/s)					
Right	15.8	8.5	23.1	< .01	14
Left	12.5	6.6	18.5	< .01	12
Median motor latency (m/s)					
Right	−1.8	−2.8	−0.8	< .01	22
Left	−1.7	−2.6	−0.7	< .01	19
Median motor conduction velocity (m/s)					
Right	7.9	−2.7	18.6	.11	5
Left	13.3	8.5	18.2	< .01	5

of GAG accumulation and improved tissue compliance.[11] Given that evidence, the lack of benefit at the carpal tunnel suggests a multifactorial etiology for development of CTS. Explanations could include (1) 14 doses of enzyme is not enough for lasting benefit, or (2) ERT does not penetrate sufficiently well into the ligaments to help, or (3) ERT reduces the tissue accumulation of GAGs but only effectively in the tissues where the enzyme has greater penetration, such as the liver.[17]

In a recent large international multicenter collaborative study of 217 HS patients, 45% underwent surgical intervention for CTS.[7] When the transplant was performed after 16 months of age, the hazard ratio for development of CTS was 1.72, suggesting a lower need for carpal tunnel surgery following transplants performed at an earlier age. The authors also note significant interinstitutional differences in indications for surgical intervention for CTS and other disease complications, a reality that may hinder the findings of such a multicenter retrospective study.

This study has several limitations. First, it is limited by its retrospective design. Second, patients were included only if they underwent nerve conduction testing and clinical consultation with the senior author (A.E.V.H.) at least once following HCT. Although it has been policy at our institution since 1990 to routinely recommend screening NCS, not all patients return for testing. This lack of uniform screening limits the ability to accurately assess the incidence of CTS in this rare syndrome.

Whereas ERT remains an effective means to reduce the accumulation of GAGs in somatic tissues of patients with HS, it did not effectively reduce the clinical risk of developing CTS when used in the peritransplant period at our center. The prevalence of CTS in patients with HS continues to be high, and routine screening with NCS testing is indicated for these HS patients. Surgical release of the transverse

carpal ligament is an effective means of preventing development of permanent deficits associated with increased pressure on the median nerve.[6]

We continue to advocate for routine screening with NCS testing in all HS children, given the early onset of CTS and the inability of young patients to express the typical adult symptoms. The data collected in this study provide evidence that surgical intervention improves the median nerve function.[18] The standard of care for patients with all mucopolysaccharidosis diseases should include evaluation and possible treatment for CTS. Further investigations into local administration of the enzyme into the carpal tunnel, or longer-term posttransplant IV ERT augmentation, may be needed to reduce the high incidence of CTS.

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