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;■(■):1.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.

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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