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Activity of daily living for Morquio A syndrome

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ABSTRACT

The aim of this study was to evaluate the activity of daily living (ADL) and surgical interventions in patients with mucopolysaccharidosis IVA (MPS IVA).
The factor(s) that affect ADL are age, clinical phenotypes, surgical interventions, therapeutic effect, and body mass index.
The ADL questionnaire comprises three domains: "Movement," "Movement with cognition," and "Cognition." Each domain has four subcategories rated on a 5-point scale based on the level of assistance. The questionnaire was collected from 145 healthy controls and 82 patients with MPS IVA. The patient cohort consisted of 63 severe and 17 attenuated phenotypes (2 were undefined); 4 patients treated with hematopoietic stem cell transplantation (HSCT), 33 patients treated with enzyme replacement therapy (ERT) for more than a year, and 45 untreated patients.
MPS IVA patients show a decline in ADL scores after 10 years of age. Patients with a severe phenotype have a lower ADL score than healthy control subjects, and lower scores than patients with an attenuated phenotype in domains of "Movement" and "Movement with cognition." Patients, who underwent HSCT and were followed up for over 10 years, had higher ADL scores and fewer surgical interventions than untreated patients. ADL scores for ERT patients (2.5 years follow-up on average) were similar with the-age-matched controls below 10 years of age, but declined in older patients. Surgical frequency was higher for severe phenotypic patients than attenuated ones. Surgical frequency for patients treated with ERT was not decreased compared to untreated patients.
In conclusion, we have shown the utility of the proposed ADL questionnaire and frequency of surgical interventions in patients with MPS IVA to evaluate the clinical severity and therapeutic efficacy compared with age-matched controls.

Abbreviations: ADL, activity of daily living; AIDHC, Alfred I. duPont Hospital for Children; BMI, body mass index; C6S, chondroitin-6-sulfate; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; GALNS, N-acetylgalactosamine-6-sulfate sulfatase; HSCT, hematopoietic stem cell transplantation; KS, keratan sulfate; LSD, lysosomal storage disease; MPS, mucopolysaccharidoses; MPS IVA, mucopolysaccharidosis IVA.

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1. Introduction

Mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome) is a lysosomal storage disorder with an autosomal recessive trait, caused by a deficiency of N-acetylgalactosamine-6-sulfate sulfatase (GALNS) [1–5]. The deficiency of this enzyme leads to systemic accumulation of the glycosaminoglycans (GAGs) keratan sulfate (KS) and chondroitin-6-sulfate (C6S), primarily in cells and extracellular matrix of cartilage [6]. Accumulation of these GAGs causes incomplete endochondral ossification, leading to characteristic skeletal features such as disproportionate dwarfism with a short trunk and neck, pectus carinatum, joint laxity, kyphoscoliosis, genu valgum, and pes planus [1,2,7–16]. Radiographic findings show dysostosis multiplex with universal platyspondyly, anterior beaking of the lumbar spine, flaring of the rib cage, tilted ulna, coxa valga, flattering femoral head, and epiphyseal dysplasia of joints [2,7,8,17–28]. Most patients become wheelchair-bound in their second decade of life and undergo multiple orthopedic surgeries to alleviate serious medical complications [14,23–25]. Common mortality and morbidity are due to spinal cord injury that leads to spinal cord compression and instability of C1–C2 joint and later, respiratory failure caused by obstructive trachea and restrictive lung [14,23–25,27–29]. Severe tracheal obstruction leads to a high mortality and morbidity [28,30,31]. Most patients with MPS IVA patients need multiple surgical procedures with a high-risk anesthetic care throughout their lives [32–36].

The surgical interventions for patients with MPS IVA include a wide range of tissues such as adenoid/tonsil, ear, mandibula, spine, trachea, hand, hip, leg, knee, and ankle, that are required at different ages of development [14,16,37].

The two major therapeutic options for MPS patients are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). When compared with ERT, HSCT showed a superior reduction in substrate burden [38,39], and was better able to ameliorate and/or cure associated musculoskeletal and organ-specific complications [40–42]. Unlike conventional ERT, HSCT can access the central nervous system and bone tissue, allowing treatment of neurocognitive degeneration [25,38,43–45] and skeletal dysplasia [46,47]. The mortality rate of the HSCT procedure for patients with MPS is now approximately 5% in a facility with well-trained staff [48, personal communication with Dr. Yabe]. Using an improved HSCT protocol [48] and by careful selection of patients and donors, the risk of HSCT is minimized. ERT for diagnosed MPS patients is currently widely accepted. Early diagnosis and early treatment provide the most benefit to the patients with MPS [49,50].

There is no therapy to cure bone lesions in MPS IVA although ERT [51–54] and HSCT [52,54–56] are available in clinical practice. Studies have shown that weekly ERT reduces urinary GAG levels and improves endurance (6-min walk test; 6MWT) and lung function [57,58]. However, in an extension trial, patients who had received placebo and subsequently received ERT for 48 weeks, did not show any improvement in the 6MWT, compared with placebo group [59]. The long-term follow-up after early introduction of HSCT has shown a therapeutic effect in amelioration of progression of the disease, suggesting that HSCT is a therapeutic option for patients with Morquio A [56]. Regardless of treatment approach, early treatment yields the most significant impact in ameliorating disease symptoms [25,52,56,60,61].

To assess the ADL in patients with MPS, several questionnaires have been designed. The Pediatric Evaluation of Disability Inventory (PEDI) is used to measure general child health [62]. The Functional Independence Measure (FIM) is widely used to evaluate ADL in patients with Hunter syndrome [22,23,62]. The PEDI and FIM questionnaire covers both motor and cognitive function. Moreover, a modified version of the Brief Assessment Examination (BAE) is used to assess cognitive functions for MPS III, which includes both ADL and evaluation of MPS-specific symptoms. [63]. However, these questionnaires need a trained professional, making the assessment inconvenient and time-consuming for the patients and their families. We have developed a simple ADL questionnaire and validated it for normal healthy children and patients with Hunter syndrome, distinguishing patients from control subjects [44]. This ADL questionnaire comprises three domains: “Movement,” “Movement with Cognition,” and “Cognition”, distinguishing it from other questionnaires comprised of, at most, two domains. We demonstrated that the ADL score correlates with clinical phenotype and therapeutic mode in Hunter syndrome and that HSCT provides a higher ADL score than ERT [44, see Supplemental Fig 1]. Early HSCT provided a higher score than late HSCT. Another advantage of this ADL questionnaire is that it can be self-administered and completed within 15 min. These findings indicated that this questionnaire could probably be applied to other types of MPS.

To date, several studies have evaluated the clinical status of MPS IVA [62,64–67]; however, the effect of ERT and HSCT on ADL and surgical interventions has not been compared with age-matched control subjects and untreated patients.

In this study, we have compared the ADL score and surgical interventions in treated, untreated, and age-matched control groups and have assessed the correlation between ADL and MPS symptom scores.

2. Subjects and methods

2.1. Subjects

All healthy controls were enrolled with informed consent at Gifu University. The MPS IVA patients were enrolled, with informed consent at Gifu University and Alfred I. duPont Hospital for Children (AIDHC). Age, gender, height and weight, ADL and MPS questionnaires, and surgical, ERT, and HSCT history were collected. Normal control subjects ($n = 145$; 72 males, 73 females; age range 0.33–43.55 years old; average age, 9.19 ± 8.00 years, median 7.08) and patients with MPS IVA ($n = 82$; 39 males, 43 females; age range, 0.71–70.46 years old; average age 22.40 ± 13.13 years, median 19.85) were enrolled. Sixty-three patients were diagnosed with a severe phenotype, and 17 patients were with an attenuated phenotype according to the criteria by height [68,69].

The FDA report indicates that a group of patients, who received placebo for 24 weeks in phase 3 clinical trial and subsequently received ERT for other 48 weeks in an extension trial, did not show therapeutic improvement of 6MWT, compared with the baseline in placebo group [58]. Therefore, patients with more than one-year ERT were defined as ERT-group. Thirty-three patients were treated with ERT including two patients who underwent corrective tracheal surgery during treatment (see below) [31], 4 patients were treated with HSCT [56], and 45 patients were untreated (including 12 patients with less than one-year ERT). In our study, the average starting age of ERT was 16.5 ± 12.7 years, and the average duration of ERT was 2.5 ± 1.0 years. The average starting age of HSCT was 10.6 ± 5.6 years, and the average observation period after HSCT was 19.0 ± 7.6 years.

Patients treated with ERT for more than one year had participated in a clinical trial [64]. Patients, who could not walk ≥30 m in a 6 min walk test (6 MWT), were not eligible to participate in the trial. Patients, who underwent surgical interventions within 3 months before initiation of ERT and had planned them during the clinical trials, were also excluded.

Therefore, patients in the ERT group did not include the most severe phenotype.

Six patients (2 patients with less than one-year ERT; 4 patients with more than one-year ERT) discontinued ERT because of either 1) adverse effects (2 patients) or 2) inability to strictly comply with the protocol (4–5 h weekly infusions, 4 patients).

For adults aged 20 years or older, body mass index [BMI: weight (kg)/height $(m)^2$] was used to determine standard weight status categories. Four categories of weight status associated with BMI for adults are classified as follows: below 18.5 as “Underweight,” 18.5–24.9 as “Normal or healthy Weight,” 25.0–29.9 as “Overweight,” and 30.0 and above as “Obese.” For children and teens, aged 2 through 19 years old, the corresponding BMI-for-age percentile was assigned based upon a