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Elevated TNF-α is associated with pain and physical disability in mucopolysaccharidosis types I, II, and VI

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Abstract

Background—Children and adults with the lysosomal storage diseases mucopolysaccharidosis (MPS) types I, II and VI live shortened lives permeated by chronic pain and physical disability. Current treatments do not alleviate these problems. Thus there is a critical need to understand the mechanism of chronic pain and disability in MPS in order to improve the way we treat patients. A potential target is inflammation.

Hypothesis—We hypothesized that excessive inflammation mediated by the tumor necrosis factor–α TNF-α) inflammatory pathway is the fundamental cause of much of the chronic pain and physical disability in MPS.

Methods—55 patients with MPS I, II, or VI were enrolled over the course of a 5-year prospective longitudinal natural history study and evaluated annually for 2–5 years. 51 healthy controls were enrolled in a separate cross-sectional study of bone and energy metabolism. TNF-α was measured by ELISA. Pain and physical disability were measured by the Children's Health Questionnaire – Parent Form 50 (CHQ-PF50). Differences in log-transformed TNF-α levels and associations with CHQ domains were evaluated using a linear mixed effects model with random intercept.

Results—TNF-α levels were measured in 48 MPS (age 5–17 years; 35% female) and 51 controls (age 8 to 17 years; 53% female). Among MPS, 22 (46%) were treated with hematopoietic cell transplantation (HCT) alone, 24 (50%) with enzyme replacement therapy (ERT) alone, and 2 (4%) with both HCT and ERT. TNF-α levels are higher in MPS compared to healthy controls ($p<0.001$). Higher TNF-α levels are associated with increased pain and decreased physical function, social limitations due to physical health, and physical summary score (all $p<0.05$). TNF-α levels were not significantly associated with the general health score. TNF-α levels did not change significantly over time in MPS.

Conclusions—Higher TNF-α levels are implicated in the pain and decreased physical function present in individuals with MPS despite treatment with ERT and/or HCT, suggesting that TNF-a inhibition could potentially be a useful adjunctive therapy. Further investigation into the role of TNF-α inhibition in MPS to decrease pain and improve physical function is indicated.

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Keywords

TNF-α; mucopolysaccharidosis; inflammation; bone; joint

Introduction

Children with the rare genetic disease mucopolysaccharidosis (MPS) continue to suffer and prematurely die from their disease. Enzyme replacement therapy (ERT) and/or hematopoietic cell transplantation (HCT) can help kids with MPS live longer, but these treatments are not cures, and only partially alleviate suffering. Neither ERT nor HCT adequately treats musculoskeletal disease, cardiac valvular disease, or central nervous system disease (1–17). For example, individuals with MPS I, II and VI treated with ERT and/or HCT have progressive skeletal disease including hip dysplasia, kyphoscoliosis, bone density deficits, and short stature that is generally resistant to treatment with growth hormone (13–15,18,19), as well as progressive joint contractures, stiffness, and genu valgum (6,8,9,11,20,21) despite these treatments. In fact, the majority of these individuals report chronic pain and have significant limitations in their activities of daily living due to their musculoskeletal disease. Thus there is a critical need to understand the causes of pain and physical disability in order to improve the way we treat MPS.

TNF-α is a potential therapeutic target. TNF-α is involved in a variety of inflammatory pathways that have destructive results such as increased endothelial permeability, inflammatory cell migration, matrix metalloproteinases (MMPs), and prostaglandins (22). Elevated levels of TNF-α and other inflammatory markers in this pathway have been reported in animal models of MPS (23–26). Importantly, decreasing inflammation through treatment of MPS animals with anti-TNF-α medications or another anti-inflammatory medication, has demonstrated improvements in mobility and exercise tolerance, resolution of joint inflammatory changes, and increased bone length (25–28). In addition, the cardiovascular disease, which is common in MPS despite treatment with ERT and/or HCT, is likely inflammatory in nature as well (2,29,30).

For this first study of the role of TNF-α in humans with MPS, based on these preclinical data, we hypothesized that 1) TNF-α levels would be higher in individuals with MPS compared to healthy controls and 2) that elevated levels of TNF-α would be associated with more severe pain and physical disability due to more severe skeletal disease and activation of inflammatory pathways. We used data from a 5-year longitudinal observational natural history study of MPS I, II and VI and from a separate cross-sectional study of bone and energy metabolism in healthy children and adolescents to test these hypotheses.

Methods

Children and adolescents with MPS aged 5–17 years were enrolled in two 5-year longitudinal observational studies and evaluated on an annual basis. Inclusion criteria included diagnosis of MPS I, II, or VI, ability to travel to the study center, and English speaking. Exclusion criteria included pregnancy and inability to comply with study procedures. A healthy cohort age 8–17 was also enrolled from the local community;

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exclusion criteria for this cohort were diabetes, medications that altered insulin sensitivity, secretion or beta cell mass, concurrent participation in an intervention trial, and pregnancy. The University of Minnesota Institutional Review Board approved both studies. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from the participants.

TNF-α levels were measured annually for 2–5 years in MPS and at one time-point in the healthy cohort. Pain and physical function were measured with the Children's Health Questionnaire – Parent Form 50 (CHQ-PF50) annually for 2–5 years in the MPS group. In MPS participants, data are included from the following number visits: 1 visit for 12 (25%) participants, 2 visits for 9 (18%) participants, 3 visits for 14 (29%) participants, 4 visits for 12 (24%) participants, and 5 visits for 2 (4%) participants.

TNF-α was measured in plasma by enzyme-linked immunosorbent assay (ELISA) at the University of Minnesota Cytokine Reference Lab. The CHQ-PF50 evaluates parent-report of both severity and frequency of their child's bodily pain and limitations in their child's physical function in activities such as play, getting around school, climbing stairs, and taking care of activities of daily living (e.g. eating, dressing, bathing, going to the toilet). BMI was calculated by weight (kg) divided by height squared (m^2).

Statistical analysis

Descriptive analyses of baseline characteristics and outcomes included means and standard deviations for continuous variables and frequencies for categorical variables. Differences in log-transformed TNF-α levels were evaluated using a linear mixed effects model with random intercept to account for the correlated nature of multiple measurements from the same individual. Similarly, associations of log transformed TNF-α with CHQ domains were also evaluated using linear mixed models with random intercept. The distribution of TNF-α levels among individuals treated with ERT versus those treated with HCT were very similar and therefore these groups were grouped together for all analyses. Statistical significance was considered as $p<0.05$. All statistical analyses were conducted using R v.3.1.1 (31)

Results

Characteristics of the MPS and healthy control cohorts are detailed in Table 1. In brief, there was a greater percent female in Controls, which is expected since MPS II is an X-linked disease. There was also a greater percent of non-white and higher body mass index (BMI) in Controls. Finally, Controls were more advanced in their pubertal stage.

TNF-α is significantly higher in children with MPS compared to healthy children (Fig 1, $p<0.001$). Higher TNF- α levels were associated with more pain, decreased physical function, increased social limitations due to physical disability, and overall decreased quality of life related to physical disability (i.e. Physical Summary Score) in MPS subjects (Table 2 and Fig 2). TNF-α levels did not change significantly over time in MPS and were not significantly associated with age or BMI.

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Discussion

Our results identify for the first time in humans with MPS, the critical role of inflammation in MPS related pain and physical disability. We found that TNF-α levels were elevated in children and adolescents with MPS and associated with more pain and physical disability. These results are consistent with pre-clinical data from MPS animal models (23–27) and suggests that treatments targeted at decreasing inflammation may improve skeletal disease and quality of life in individuals with MPS.

Glycosaminoglycan (GAG) accumulates in all tissues in MPS due to deficiencies in enzymes required for GAG degradation. The mechanism of elevated TNF-α levels in MPS is likely related to this excess of GAG that stimulates macrophage via toll-like receptor 4 (TLR-4) (26) triggering multiple downstream inflammatory effects. TNF-α is a key player in a variety of inflammatory pathways originating from macrophage stimulation. Downstream effects of TNF-α include the recruitment of neutrophils and increasing endothelial permeability, which drives local inflammation, and the release of additional inflammatory cytokines such as prostaglandin E2 which can contribute to pain (22). In addition, increased TNF-α is associated with increased osteopontin, a regulator of inflammation, bone mineralization and activation of macrophage (32,33), and osteopontin has also been shown to be elevated in serum of nine children with MPS (34). Combined, these effects likely explain the associations found in our population of TNF-α levels with pain and physical disability.

Chronic inflammation can result in multiple detrimental effects. In MPS, inflamation likely also explains, at least in part, the elevations previously described in markers of bone and cartilage turnover, as well as deficits in bone mineral content (14,35). Inflammation, and specifically TNF-α, causes resistance to growth hormone (36) and thus may be similarly contributing to the short stature with resistance to treatment with recombinant human growth hormone reported in individuals with MPS (13,15,18). In other words, the inflammation caused by chronic activation of the TNF-a pathway may underlie much of the poor growth, skeletal malformations, and painful orthopedic disease that MPS patients suffer.

TNF-α is a potential therapeutic target. TNF-α inhibition improves physical function and skeletal disease in animal models of MPS. Specifically, a study in rats with MPS VI, using a rat specific inhibitor of TNF-α in combination with ERT, found functional benefits of the addition of TNF-α inhibitor treatment: compared to MPS VI rats treated with ERT alone, MPS VI rats treated with both a rat-specific TNF-α inhibitor and ERT beginning at 21 days of life had significantly faster and more coordinated strides and increased duration of time on an accelerating rotarod apparatus (25). MPS VII mice interbred with toll-like receptor 4 knock-out mice have normalization of TNF-α and an improvement in rotarod performance as well(26). Finally, treatment of MPS VI rats with infliximab (a TNF-α inhibitor) results in decreased inflammatory biomarkers, improvement in joint inflammatory changes (i.e. synovial invasion of bone), and a reduction in chondrocyte apoptosis (25). Additionally, treatment with the anti-inflammatory pentosan polysulfate can decrease TNF-α and also results in improvements in mobility and skeletal disease in an animal model of MPS VI (27,28).

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This study is primarily limited by the subjective measure of pain and physical function and that the CHQ-PF50 is a parent, not patient, reported outcome. Future studies should include an objective measure of physical function such as range-of-motion testing. In addiiton, although the CHQ-PF50 is a well established measure in other populations, it has not been validated in MPS populations. Finally, there were some small differences between controls and MPS subjects (e.g. sex, age, and race); however, TNF-α was not associated with age (p=0.950) and therefore we did not believe it necessary to adjust for these differences given the statistically small sample size.

In conclusion, there is no effective treatment for skeletal disease in MPS. Our findings of an association between elevated TNF-α level with pain and physical disability support the study of anti-inflammatory medications in the treatment of MPS I, II, and VI. Treatment with an anti-inflammatory has the potential to shift the current clinical practice paradigm for treatment of MPS, focused solely on decreasing GAG storage through ERT and/or HCT, to a multi-faceted approach targeting both GAG and inflammation reduction. Improved treatment of skeletal disease that causes pain and physical disability in MPS could not only improve quality of life, but also prevent multiple orthopedic procedures and long-term obesity and other metabolic disease associated with inactivity.

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Highlights

- Chronic inflammation in the mucopolysaccharidosis (I, II, and VI) is described.
- Higher inflammation (tumor necrosis factor-alpha [TNF-α]) is associated with pain.
- Higher inflammation (TNF-α) is associated with physical disability.

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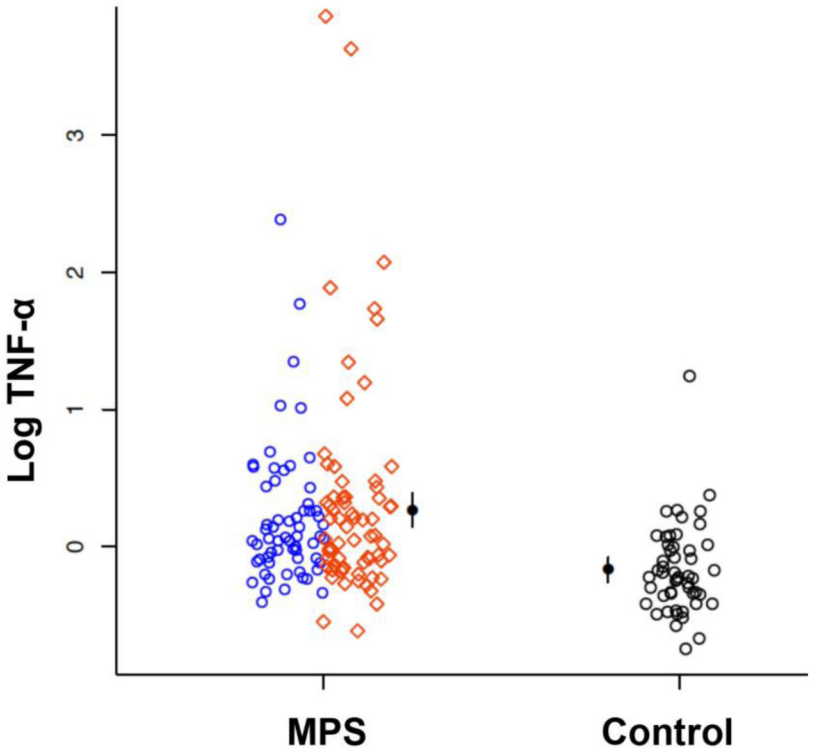

Fig 1. Comparison of TNF-α levels (repeated measurements over 2–5 years) in MPS (blue circles=HCT treated; red diamonds=ERT treated) versus healthy controls

Mean and 95% confidence intervals are indicated by filled circle and vertical lines.

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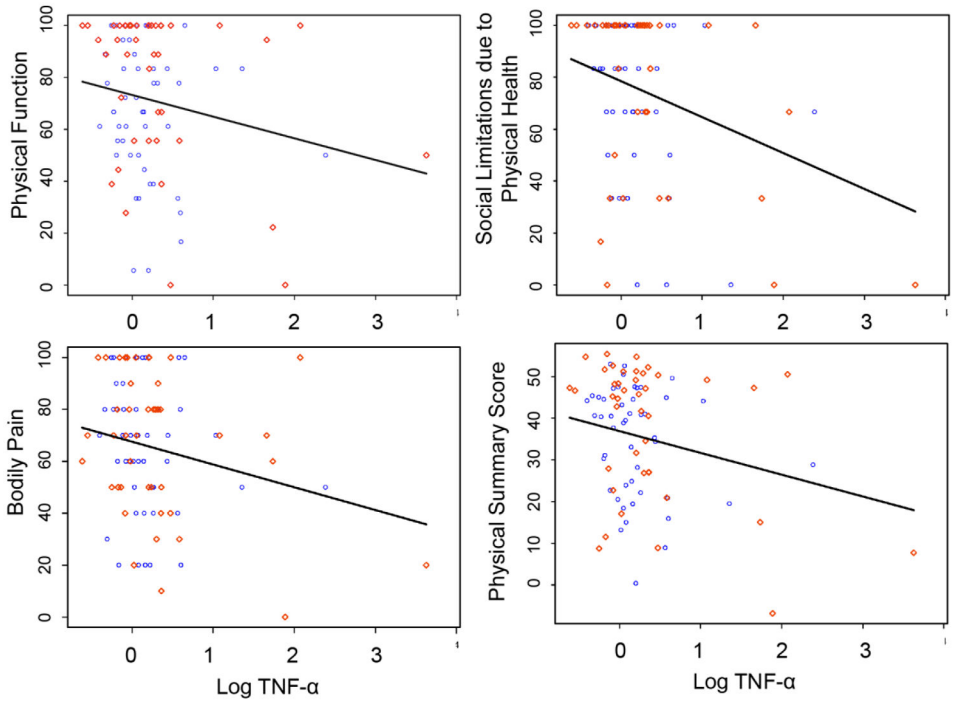

Fig 2.

Associations between TNF-α levels (repeated measurements over 2–5 years) and Children's Health Questionnaire-Parent Form 50 (CHQ-PF50) outcomes in MPS (blue circles=HCT treated; red diamonds=ERT treated).

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Table 1

Population characteristics at baseline. Mean±SD or N(%) are presented.

Covariate	Control (N=51)	MPS (N=49)	MPSIH (N=22)	ERT MPS (N=27)
Female	27 (53%)	17 (35%)	13 (59%)	4 (15%)
Male	24 (47%)	32 (65%)	9 (41%)	23 (85%)
MPS IH *	0 (0%)	22 (45%)	22 (100.0%)	0 (0.0%)
MPS IA	0 (0%)	8 (16%)	0 (0%)	8 (30%)
MPS II	0 (0%)	12 (25.%)	0 (0%)	12 (44%)
MPS VI *	0 (0%)	7 (14%)	0 (0%)	7 (26)
Race				
White	33 (64%)	45 (92%)	22 (100%)	23 (84%)
Black	5 (10%)	1 (2%)	0 (0%)	1 (4%)
American Indian	1 (2%)	1 (2%)	0 (0%)	1 (4%)
Asian or Pacific Islander	0 (0%)	1 (2%)	0 (0%)	1 (4%)
Other or mixed	7 (14%)	1 (2%)	0 (0%)	1 (4%)
Unknown/not reported	5 (10%)	0 (0%)	0 (0%)	0 (0%)
Tanner Stage **				
- 1	3 (6%)	25 (51%)	13 (59%)	12 (44%)
- 2 or 3	9 (18%)	8 (16%)	4 (18%)	4 (15%)
- 4 or 5	39 (76%)	14 (28%)	5 (23%)	9 (33%)
Age	14.6 (2.0)	11.2 (4.3)	9.4 (3.30)	12.7 (4.5)
BMI **	27.1 (8.6)	19.8 (4.6)	18.6 (3.93)	20.8 (4.9)
Bone age **	15.1 (2.1)	10.0 (4.7)	8.9 (4.05)	10.9 (5.0)
TNF-alpha	0.9 (0.4)	2.4 (6.7)	1.4 (1.11)	3.1 (9.0)

MPS=mucopolysaccharidosis, ERT=enzyme replacement therapy, BMI=body mass index, TNF-alpha=tumor necrosis factor - alpha

* All MPS IH treated with HCT, 2 MPS VI treated with HCT, remainder of subjects treated with ERT for >1 year.

** missing data on Tanner stage and bone age in two and BMI in one MPS subject(s).

MPS=mucopolysaccharidosis; IH=Hurler syndrome; IA=Hurler-Scheie or Scheie (attenuated); II=Hunter syndrome; VI=Maroteaux-Lamy syndrome; BMI=body mass index

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Table 2

Worsening pain and other QOL outcomes (measured by the CHQ-PF50) per doubling of TNF-α level * in children and adolescents with MPS (data shown in Fig 2).

Outcome	Nobs, N	Change in CHQ Score per doubling TNF-α (95% CI)	P-value
CHQ: Physical Functioning	94, 39	−5.79 (−11.20, −0.38)	0.036
CHQ: General Health	88, 38	−0.61 (−3.72, 2.51)	0.703
CHQ: Social Limitations Due to Physical Health	94, 39	−9.60 (−15.94, −3.26)	0.003
CHQ: Bodily Pain	94, 39	−6.09 (−10.98, −1.19)	0.015
CHQ: Physical Summary Score	88, 38	−3.62 (−6.28, −0.96)	0.008

QOL=quality of life; CHQ=PF50=Children's Health Questionnaire-Parent Form 50; MPS=mucopolysaccharidosis; Nobs=total number of observations; N=number of subjects

* TNF-α levels are from repeated measurements over 2–5 years