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I, Farrah R Mahan B.A., hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

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Pain and Fatigue Associated with Generalized Joint Hypermobility in Gaucher Disease

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Pain and Fatigue Associated with Generalized Joint Hypermobility in Gaucher Disease

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ABSTRACT

Gaucher Disease (GD) is an autosomal recessive inherited lysosomal storage disease that can cause symptoms such as hepatosplenomegaly, pulmonary disease, fatigue, and bone pain and crises. Treatment is primarily through enzyme replacement therapy or substrate reduction therapy. While most physicians show concern with improving visceral and hematologic symptoms, patients report interest in decreasing fatigue and pain, which has an effect on quality of life. Observed abnormalities in cytokine secretion in GD patients have been shown. Excess cytokines are known to cause tissue damage, bone remodeling, and increased inflammation. Generalized joint hypermobility (GJH) is characterized by joint laxity and increased joint range, and has also been seen to affect levels of both pain and fatigue. Physical therapy is the recommended treatment.

This study investigated the relationship in patients with GD between chronic pain, residual fatigue, and GJH. Focused on patients at CCHMC who have GD Type 1, participants performed a Beighton Score and five-part questionnaire to meet diagnostic criteria for GJH. The Brief Pain Inventory (BPI) and Fatigue Severity Scale (FSS) were used to assess levels of pain and fatigue. Therapeutic goals and the Disease Severity Scoring System (DS3) were used to evaluate treatment goals and disease involvement.

Through our collection of data, we found 33% of our population of 12 participants met GJH criteria. Of those with GJH, 50% expressed moderate pain severity and 25% reported moderate pain interference, compared to 12.5% and 0% of those without GJH for severity and interference, respectively. Similarly, 50% of participants with GJH reported severe fatigue as well as 50% of participants without GJH. These

findings were not statistically significant. However, there was a strong positive correlation between reported values of pain severity, pain interference, and fatigue. Patients tended to report higher levels of one value if they reported higher levels of another. Participants were found to meet a median of 96.3% of Gaucher-related therapeutic goals. In those with GJH versus those without GJH, 50% and 57.1%, respectively, were categorically assessed as having a “mild disease” involvement. Associations were not statistically significant.

The goal of the study was to determine if patients with GD who have GJH experience more pain and fatigue than those who do not have GJH. Current literature supports that 2-57% of the general population has GJH, while our study found 25% of our population. We did not see a significant change in the levels of pain and fatigue between the two groups of participants, but the study did reinforce that those who report higher levels of pain severity and interference also report high levels of fatigue, regardless of a GJH diagnosis. With that in mind, someone with high levels of pain may also need to have anticipatory management for fatigue. Our patients were also well-managed and met many therapeutic goals, which may account for the levels of pain and fatigue reported. Future studies recommended include larger, more generalizable studies for GD and GJH.

Gaucher Disease, Generalized Joint Hypermobility, Pain, Fatigue, Beighton Score, Five-Point Questionnaire, Fatigue Severity Scale, Brief Pain Inventory

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INTRODUCTION

Gaucher Disease

Gaucher Disease (GD) is an inherited lysosomal storage disease that affects approximately 1 in 60,000 live births, making it the most common lysosomal storage disease (Meikle, Hopwood, Clague, & Carey, 1999). GD results from a deficiency of the lysosomal enzyme glucocerebrosidase, within macrophages, and aids in the breakdown of glucosylceramide. GD is characterized by storage of this fatty substance in macrophage-rich organs, resulting in hepatosplenomegaly, bone marrow infiltration, and pulmonary and neurologic dysfunction. Storage also causes chronic inflammation, pain, and fatigue (National Institute of Neurological Disorders and Stroke, 2016). Diagnosis of GD is confirmed by demonstrating a deficiency of glucocerebrosidase enzyme activity, with or without detecting two pathogenic mutations in the *GBA* gene, located on chromosome 1q21, which is the only gene identified to cause GD. Over 400 mutations in the *GBA* gene have been identified. These mutations are inherited in an autosomal recessive fashion and are caused by homozygous or compound heterozygous mutations in the *GBA* gene. In GD, the most common mutation is L444P and the most common genotype is N370S/L444P. Of patients with Ashkenazi Jewish ancestry, at least 70% have been found to have at least one copy of the N370S allele (Mistry et al., 2011).

Symptoms

GD symptoms vary from one individual to the next. Historically, there are three subtypes of GD, which are categorized by the presence or absence of primary central nervous

system involvement. GD Types 2 and 3 are characterized by problems that affect the central nervous system, such as seizures and progressive brain involvement. GD Type 2 has an earlier onset and a more rapid progression. GD Type 1 is typically believed to be central nervous system sparing. However, recent research has found an association between GD and Parkinsonism and neuropathy (Rosenbloom et al., 2011). GD Type 1, seen in more than 90% of all patients affected by GD, is also associated with splenomegaly, hepatomegaly, cytopenia (with or without anemia, thrombocytopenia, or leukopenia), and pulmonary disease. Other symptoms include bone disease, bone pain, secondary neurologic disease, and coagulation, immunologic, and metabolic abnormalities (G.M. Pastores & Hughes, 2000). Although the onset of symptoms in GD Type 1 can appear at any age, most patients report their first symptoms before adulthood (Mistry et al., 2011).

Treatments & Limitations

There are two primary treatments for GD. Most commonly, patients are treated with enzyme replacement therapy (ERT) (Brady, 1966). This treatment replaces the deficient enzyme glucocerebrosidase with a modified copy of the enzyme, which is taken up intracellularly. ERT is administered via biweekly infusions in a clinic or home setting. ERT has been proven to decrease liver and spleen size, as well as increase hemoglobin and platelet counts (Beutler, 2004; Grabowski). Another treatment for GD is substrate reduction therapy (SRT). This treatment's primary goal focuses on decreasing the amount of glucosylceramide present by preventing its synthesis (Cox et al., 2000; Mistry et al., 2015; Smid, Ferraz, Verhoek, & Mirzaian, 2016).

With either treatment, some patients do not experience a significant decrease in chronic bone pain or residual fatigue. Patients reported that these symptoms, in particular, have a devastatingly negative effect on their quality of life. Specifically, a negative outlook on health tends to negatively affect views on social life (Hayes, Grinzaid, Duffey, & L. J. Elsas, 1998).

Inflammation within Gaucher Disease

It has been observed that there are abnormalities in cytokine secretion in patients with GD. Cytokines, which are molecules which aid in cell communication and encourage movement to sites of inflammation, are secreted in excess throughout the body of patients with GD due to an accumulation of glucocerebrosidase. Excess cytokines are known to cause tissue damage, bone remodeling, and result in increased inflammation (Aflaki et al., 2016; Tantawy, 2015). In the absence of typical inhibitory signals, which are inhibited by the accumulation of glucocerebrosidase, cytokines promote connective tissue alterations, which may result in permanent changes to tissue structure and function (Kovacs & Dipietro, 1994).

Generalized Joint Hypermobility

Joint hypermobility has been defined as the “capability [of] a joint (or a group of joints) to move, passively and/or actively, beyond normal limits along physiological axes” (Castori et al., 2017). Specifically, generalized joint hypermobility (GJH) is the term used when joint hypermobility is indicated in more than five joints. GJH falls under the term Hypermobility Spectrum Disorder, which is included in the Ehlers-Danlos Syndromes. Ehlers-Danlos Syndromes

are a group of heritable connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. While not all subtypes of the Ehlers-Danlos Syndromes have distinct pathologies identified, it is assumed that it is a consequence of alterations in fibrous collagen genes or in genes that encode collagen modifiers (Malfait et al., 2017). GJH is fairly common, with research citing from 2-57% of participants affected with a variety of genetic backgrounds, and higher incidences among females than males. Current literature supports the prevalence of GJH as between 6-57 % for women and 2-35 % for men (Remvig, Jensen, & Ward, 2007; Russek & Errico, 2016).

GJH can present without additional symptoms other than joint hypermobility, which may reflect the large range of those affected. When GJH is accompanied by symptoms, it can include complications of joint instability, musculoskeletal pain, skin involvement, and reduced quality of life (Scheper et al., 2016).

Diagnosis of GJH is primarily measured through the Beighton Score, which clinically assesses joint hypermobility through the use of a 9-point scale, looking at first finger opposition, fifth finger extension, elbow extension, knee extension, and back forward bending. This is supplemented by the five-part questionnaire (Beighton, Solomon, & Soskolne, 1973). Gender, age, ethnicity, and physical activity have been known to influence these scores (Remvig et al., 2007).

Treatment for GJH is symptomatic, as there is no cure. As with other Ehlers-Danlos related syndromes, most physicians suggest physical therapy or physical activity, using braces to improve joint stability, and taking medications that help control pain (Rombaut et al., 2011).

Gaucher Disease and Joint Hypermobility

GD and GJH type have overlapping symptoms of chronic pain and fatigue. While GD's pathology is due to a deficiency of a certain enzyme, GJH's pathology is due to an assumed alternation in collagen. Therefore, depending on the origin of the pain and fatigue the management would be expected to be different. Specifically, if a patient with GD continues to have pain and fatigue despite treatment with ERT or SRT, and the symptoms are a result of hypermobility, then higher doses of Gaucher related therapies would not be expected to improve these symptoms. However, therapies directed to hypermobility, such as physical therapy and pain management may be more beneficial.

Significance of Study

There is no current information regarding the prevalence of GJH in those with GD. Furthermore, there is little information regarding other sources of pain and fatigue for those with GD. We sought to determine how many patients with GD managed with a primary therapy for GD, such as ERT and SRT, are found to meet diagnostic criteria for GJH. We also sought to determine if GD patients who meet clinical criteria for GJH are more likely to experience significant levels of pain and fatigue than patients with GD who do not meet clinical criteria for GJH.

DESIGN AND METHODS

Participants

Eligible participants included patients with GD evaluated at Cincinnati Children's Hospital Medical Center. Patients were excluded who could not read, write, and speak English, were under five years of age, and were not on ERT or SRT treatment for GD. All study activities were approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

Each eligible participant was called. A scripted overview of the study including goals and procedures was explained. Those providing verbal consent to participate were mailed a study packet. This packet included a cover letter, instructions for completing the Beighton Score, five-part questionnaire, Brief Pain Inventory, and Fatigue Severity Scale. Photographs of patients demonstrating various parts of the Beighton Score were emailed by participants to a secure email address. The photographs were reviewed by a trained evaluator. Questions were directed to an expert physician in the treatment and management of GJH. Participants mailed the completed study packet back to the research team. Return of the packet implied consent to participate. A thorough chart review was completed for each participant returning the packet. Specific attention was paid to GD severity, treatment, pain, and fatigue. Participants who had not sent their study packet back in one month received one reminder call.

Measures

To determine a diagnosis of GJH, we asked participants to perform the Beighton Score, which is used to clinically diagnose syndromes of hypermobility. Instructions and sample photos were included to aid in the performance and photographing of the Beighton Score. A physician

decided who met criteria for GJH based on the photos participants took. The score is obtained through:

- a) Passive dorsiflexion of the little fingers beyond 90°; one point for each hand;
- b) Passive apposition of the thumbs to the flexor aspect of the forearm; one point for each hand;
- c) Hyperextension of the elbows beyond 10°; one point for each elbow;
- d) Hyperextension of the knees beyond 10°; one point for each knee; and
- e) Forward flexion of the trunk with knees fully extended so that the palms of the hand rest flat on the floor; one point.

Gender, age, ethnicity, and physical activity have been known to influence these scores (Remvig et al., 2007). It is proposed that diagnosis of GJH with the Beighton Score is ≥ 6 for prepubescents, ≥ 5 for pubertal adults up to the age of 50, and ≥ 4 for those above 50 years of age (Malfait et al., 2017). Supplementation of a five-part questionnaire was used in patients with acquired joint limitations that may affect the Beighton Score. If the Beighton score is 1 point below the age cut-off and the five-part questionnaire has at least two positive items, then GJH could still be diagnosed (Hakim & Grahame, 2003). The five-point questionnaire is as follows:

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself “double-jointed”?

Participants completed two surveys. The Brief Pain Inventory (BPI) is a 9 question scale that determines pain severity. Pain is assessed using a Likert scale from 1 to 10. Responses options for each question are a pain score of 1–4 (mild pain), a score of 5–6 (moderate pain),

and a score of 7–10 (severe pain). These scores are averaged to determine pain severity and pain interference in life, separately. The Fatigue Severity Scale (FSS) is also a 9-item survey which measures the severity of fatigue. Response options are on a Likert scale from 1 (disagree) to 7 (agree). Fatigue is assessed by calculating the mean score for each individual. A score of four or more indicates severe fatigue. Both scales are validated in chronic illnesses (Celletti et al., 2012; Güngör et al., 2013; Hoffmann et al., 2005; Mistry et al., 2015; Tan, Jensen, Thornby, & Shanti, 2004).

Finally, a chart review on participants' diagnosis and treatment history was conducted. This review included demographics, diagnosis and treatment history, and therapeutic goals relevant to GD. The records were abstracted using a medical abstraction form that is seen in the appendix. Identification numbers linked medical data to completed surveys. A report was put forth in 2004 to assess "evidence-based, therapeutic goals with reference to each organ system" in regards to the primary treatment of GD Type 1. This report outlined various goals that each patient and physician pair should achieve during the course of treatment (G. M. Pastores et al., 2004). To assess treatment outcomes, these goals were used. The Disease Severity Scoring System (DS3) is a validated survey that was used to quantify disease status and change over time. The DS3 is an 11 item scale that is filled out by a physician and is averaged across three domains: bone, hematologic, and visceral. The averages of these three scores are summed to interpret disease as borderline to mild disease (0-3), moderate disease (3-6), marked disease (6-9), and severe disease(9+) (Weinreb et al., 2010). Assessments of the DS3 were taken at each participant's initial and most recent clinical visit.

Data Analysis

Statistical analyses were performed using JMP Genomics 8.0 statistical software (SAS, Cary, NC). Continuous data are expressed as median and range. Categorical data are expressed as frequency and percentage. Participants were dichotomized through meeting criteria for GJH. Pain severity, pain interference with a participant's life, and fatigue levels assessed by the BPI and FSS, respectively, were analyzed using Fisher's exact test, due to cell numbers of contingency tables less than 5. The correlation among pain severity, pain interference with a participant's life, and fatigue was calculated through Spearman's Rho test for correlations. Two-tailed p-values < 0.05 were considered significant. Bonferroni correction for multiple testing was used for Spearman's Rho test when $\alpha=0.0167$ ($0.05/3$).

RESULTS

Demographics

Out of 100 eligible participants, 44 verbally consented and were sent survey packets. During the follow-up process, two declined to further participate in the study. Out of 42 patients consented, 16 completed surveys were received and 4 participants were removed due to exclusion criteria. Participant characteristics are summarized in Table 1. Of those participating, 7 (58.3%) were female and the median age was 46 (range 16-81). All participants were white and 6 (50.0%) reported Ashkenazi Jewish ancestry in their family history. In total, 7 participants had at least one N370S mutation (58.3%), and of those 1 was homozygous for N370S (8.3%). Half of the participants (50.0%) were on SRT at the time and their median score on their DS3 was 0.40 with a range of 0.00-4.33 at their latest clinic visit.

Generalized Joint Hypermobility

In this study, 4 (33.3%) patients out of the total 12 met criteria for GJH using the Beighton Score and supplementation of the five-part questionnaire. Of the 4 identified, 3 (75%) were female, 2 (50.0%) were on SRT, and 2 (50.0%) were on ERT.

Brief Pain Inventory

Participants with GJH were believed to report pain severity and pain interference at higher levels. A visual representation of these results is found in Table 2 and Table 3. Of those identified to have GJH, 2 (50.0%) scored mild and 2 (50.0%) scored moderate for pain severity. Participants without GJH reported mild pain severity more often than moderate with 7 participants (87.5%) and 1 participant (12.5%), respectively. This difference was found to be not significant with $p=0.236$. For pain interfering with a participant's life, 3 (75.0%) of those with GJH reported to have mild interference and 1 (25.0%) reported moderate interference. All 8 (100%) participants without GJH reported only mild pain interference in their life. Using Fisher's exact test, the difference in pain was not significant with $p=0.333$.

Fatigue Severity Scale

Participants with GJH were also thought to report higher levels of fatigue than those without GJH. Table 4 summarizes the reported fatigue data. In the GJH group, 2 (50.0%) reported mild fatigue and the remaining 2 (50.0%) reported severe fatigue. In those without GJH, 4 (50.0%) participants reported mild fatigue and 4 (50.0%) reported severe fatigue. This was found not to be significant with $p=1.00$.

Comparison of Pain and Fatigue

When comparing both BPI and FSS raw scores, a trend was observed. When participants reported higher levels of pain severity, they also tended to report higher levels of fatigue. A Spearman's Rho test showed a strong positive correlation ($\rho^2=0.703$, $p=0.011$), see Table 5. Furthermore, when the level of pain interference a participant reported is compared to their reported level of fatigue, a strong correlation is also observed ($\rho^2=0.938$, $p<0.001$), see Table 6. Comparing the levels of pain severity and pain interference reported by participants in the study shows a strong positive correlation in their relationship, as well ($\rho^2=0.809$, $p=0.001$), see Table 7. This finding supports the thought that pain and fatigue are closely related, and may influence one another.

Medical Chart Review

A chart review was conducted to assess therapeutic goals and disease severity levels. Table 8 represents these values. One patient was not assessed due to lack of chart assess. In the population, our participants had a median of 96.3% of therapeutic goals met, with a range of 88.0% to 100%. Overall, 5 (45.5%) of participants met all therapeutic goals. Breaking that down, those with GJH had a median of 98.1% of goals met (96.0%-100%), and those without GJH had a median of 92% of goals met (88.0%-100%). These findings support that current and previous patients are well managed with their current primary treatment for GD Type 1. Participants' DS3 levels at their initial clinic visit showed a median of 2.33 (0-7.73) and at their last clinic visit showed a median of 0.4 (0-4.33), considering both of those raw numbers to be categorically assessed as "mild disease" involvement. At participants' initial clinic visit, those

with GJH were scored as having a mild disease in 2 participants (50.0%) and moderate disease in the remaining 2 participants (50.0%). In those without GJH, 4 (57.1%) were classified with mild disease, 2 (28.6%) were classified with moderate disease, and 1 (14.3%) was classified as marked disease involvement. Associations between the two groups were not significant ($p=0.632$). Comparing the categorical scores of the latest visit DS3 between those with GJH and those without GJH did not show significance ($p=0.491$) with all 4 participants (100%) with GJH considered to have a mild disease involvement while 5 participants (71.4%) and 2 participants (28.6%) of those without GJH were considered to have mild and moderate disease involvement, respectively.

DISCUSSION

The overarching aim of the study was to determine if patients with GD who have GJH experience more pain and fatigue than those who do not have GJH. We hoped to find significance in our results to help better treat patients here at CCHMC and elsewhere. While our study did not answer that question at this time, it did provide us opportunities to learn from the data collected.

As formerly mentioned, the current literature is inconsistent on a specific number for the prevalence of GJH, citing from 2-57%. However, all sources agree that it is undoubtedly common. In our study, we saw 25% of participants with GJH. We can hypothesize from these findings that a large portion of our patient population may also have symptoms of GJH. In that way, we would not expect higher doses of Gaucher related therapies to be a valuable option for

those with high levels of pain and fatigue due to hypermobility. We as healthcare professionals need to make sure we are prescribing correct and effective treatments.

We question why we may not have seen the high levels of pain and fatigue that we expected in those with GJH compared to those without GJH. It may be that those without GJH also report higher levels due to GD that those with GJH may have due to hypermobility. These two groups have not been previously compared, so literature could not help us anticipate results. We did not see a significant change in the levels of pain and fatigue between the two groups of participants, but it did reinforce that those who report higher levels of pain in severity and interference also report high levels of fatigue, regardless of a GJH diagnosis. With that in mind, we can expect that someone in a clinical setting with high levels of pain may also need to have anticipatory management for fatigue.

Our participants were well managed and achieved a high number of therapeutic goals and low disease severity scores. In that sense, we would not expect patients to experience high levels of pain and fatigue. It begs the question why we, historically, have some patients still reporting higher than expected levels of pain and fatigue. While GD is a condition that is known to produce higher levels of pain and fatigue than the general unaffected population, meeting therapeutic goals should aid in alleviating those symptoms. With patients being our top priority, their top priority is pain and fatigue management, which makes it by association our main concern.

There were several limitations to our study. Most noticeably, we had a small sample size and lower than expected power in our study that did not allow us to accurately assess the questions we posed. Our convenience sample included any patient who had been evaluated at

CCHMC. This means that people who felt they could gain the most may have participated, whether that be the people who are not affected as much or those without GJH. One of our main focuses was trying to evaluate how many patients with GD had GJH. Many reported they felt they may not have meaningful information since they didn't feel they had symptoms of GJH or noticeably high levels of pain and fatigue. We also had outdated contact information and patients who were no longer being followed at the time of the study. Due to this, not all eligible participants could be contacted. We also did not always have updated medical records on participants, since not all eligible patients were currently being followed by our clinic. Finally, most participants were of similar backgrounds, and results were largely not generalizable to the large population of GD patients.

Future studies with a greater number and variety of ages, sex, and races would be more robust and increase the generalizability. As mentioned before, our small sample size did not allow our questions to be fully answered in either regard. We would also propose a longitudinal, prospective study that could follow patients over their lifetime. This study could more accurately assess patients' levels of pain and fatigue throughout their disease course and could identify symptoms of hypermobility and GJH when they first arise. As a more immediate study, Beighton scores of all current patients could be taken and BPI and FSS could be assessed at the same time, to allow an assessment of a clinic's population of hypermobility incidence and severity.

Looking ahead, we still have many more questions to answer. Patient's symptoms can have a devastating effect on their view of life. It is our job as healthcare professionals to properly assess and treat those symptoms to the best of our ability. The focus of this study was

to understand how GD and GJH may overlap in our patients, and furthermore to assess the levels of pain and fatigue between those two conditions. While our questions weren't answered yet, we know that more research will always need to be done to provide optimal care for patients, and that research like this can lead us into the correct direction.

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TABLES

Table 1. Demographics of Participants

		<i>Frequency (Percentage)</i>
Sex		
	<i>Male</i>	5 (41.7)
	<i>Female</i>	7 (58.3)
Race		
	<i>White</i>	12 (100)
Genotype		
	<i>N370S/N370S</i>	1 (8.3)
	<i>N370S/Other</i>	6 (50.0)
	<i>Other/Other</i>	5 (41.7)
AJ Ancestry		6 (50.0)
Treatment Type		
	<i>ERT</i>	6 (50.0)
	<i>SRT</i>	6 (50.0)

Table 2: Brief Pain Inventory Pain Severity Scores

Table 3: Brief Pain Inventory Pain Interference Scores

Table 4: Fatigue Severity Scale Scores

Table 5: Correlation of Pain Severity and Fatigue

Table 6: Correlation of Pain Interference and Fatigue

Table 7: Correlation of Pain Interference and Pain Severity

Table 8: Medical Chart Review Information

	Median (Range) n=7	Median (Range) n=4
	Without GJH	With GJH
Pre DS3	1.73 (0-7.73)	3.10 (1.67-3.87)
Post DS3	0.40 (0-4.33)	0.40 (0-2.07)
Therapeutic Goals Met	92.0% (88.0%-100%)	98.1% (96.0%-100%)