Increased rates of spinal fusion surgery in patients with hereditary hemochromatosis: a five-year propensity matched cohort analysis

Alex M. Kesler[a], Paul T. Kröner[b], Karn Wijarnpreecha[b] and William C. Palmer[a,b]

Object Spinal arthropathy is associated with hereditary hemochromatosis and has been linked to calcium pyrophosphate dehydrate crystal deposition (CPPD) which resembles ankylosing spondylitis on radiograph, yet lacks clinical findings of inflammatory spinal arthritis. The aim of our study was to assess the use of spinal surgery and its outcomes in the US inpatient population with hereditary hemochromatosis from 2012 to 2016 by using the US Nationwide Inpatient Sample (NIS) database.

Methods The observational retrospective cohort study uses the NIS 2012 to 2016. All patients with hereditary hemochromatosis were included using International Classification of Diseases 9th and 10th revisions, Clinical Modification codes. The cohort was stratified according to having undergone spinal surgery and substratified by the type of surgery. The primary outcome was determining the use of spinal surgery in patients with hereditary hemochromatosis. Secondary outcomes were determining length of hospital stay and total hospital charges and costs.

Results A total of 39 780 patients with hereditary hemochromatosis were identified and propensity matched to nonhereditary hemochromatosis controls. The mean patient age was 61 years, and 65% were females. For the primary outcome patients with hereditary hemochromatosis underwent significantly more spinal fusion surgery compared to patients without hereditary hemochromatosis odds of 2.13 ($P = 0.05$). While there was no difference in mean LOS, or costs, patients with hereditary hemochromatosis had higher hospital charges.

Conclusion Hereditary hemochromatosis is associated with higher odds of spinal fusion. It is a major complication not improved by phlebotomy, and there are currently no therapies to prevent this joint disease. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Arthropathy in hereditary hemochromatosis is characterized by a chronic progressive arthropathy which can be difficult to distinguish between osteoarthritis or inflammatory arthritis such as seen in rheumatoid arthritis (RA) [1]. Schumacher [2] first described arthropathy primarily affecting the second and third metacarpophalangeal (MCP) joints as a key component of hereditary hemochromatosis in 1964. The arthropathy associated with hereditary hemochromatosis was soon found to affect the hips, ankles, elbows, shoulder, and knees in addition to the MCP joints, with estimates of prevalence ranging from 24 to 81% of patients with hereditary hemochromatosis [1,3]. Spinal arthropathy associated with hereditary hemochromatosis was first described by Bywaters *et al.* [4] in 1971 in seven patients as calcium pyrophosphate dehydrate crystal deposition (CPPD) confined to the cervical and lumbar disks and ligamentum flavum which resembled ankylosing spondylitis on radiograph, yet patients lacked the inflammatory changes and symptoms of back pain. Interestingly, Bywaters *et al.* [4] found that vertebral discs did not stain positively for iron, and joint degeneration was not improved by phlebotomy. The impact of arthropathy of patients with hereditary hemochromatosis is well studied, with data showing that patients often present first with symptoms of joint pain up to nine years prior to diagnosis. Additional data suggest that hereditary hemochromatosis is associated with increased odds of undergoing joint replacement, and that arthropathy is one of the few complications of hereditary hemochromatosis which is not improved by phlebotomy [1,4–12]. However, data on the impact of spinal arthropathy are scant, particularly in regards to population-based data and addressing disease outcomes. The aim of our study was to assess the use of spinal surgery and its outcomes in the US inpatient population with hereditary hemochromatosis from 2012 to 2016 by using the US Nationwide Inpatient Sample (NIS) database.

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Departments of [a]Medicine and [b]Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA

Correspondence to William C. Palmer, MD, Davis 6FL/GI 4500 San Pablo Rd S Jacksonville, FL 32224, USA
Tel: +1 904 953 2814; fax: +1 904 953 7366; e-mail: palmer.william@mayo.edu

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Methods

Study design and data source

All patients included in our retrospective cohort study were selected from the NIS, a database developed and maintained by the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research

and Quality. The NIS is the largest publically available, inpatient, all-payer database in the USA. For each year, the database contains data on more than seven million hospital stays, which is a 20% stratified sample of more than 4000 nonfederal acute care hospitals in 45 states of the USA, which after applying respective discharge weights provided by HCUP is representative of 95% of all national hospital discharges [13].

The principal diagnosis is defined as the primary diagnosis at the time of the patient's discharge. The NIS dataset includes the principal diagnosis and up to 30 secondary diagnoses depending on the year of publication, which correspond to the patient's comorbidities. The dataset also contains 15 procedural codes for procedures performed during the patient's hospital stay, and well as length of stay (LOS) measured in days, total hospitalization charges, and other outcome measures used to calculate inpatient disease prevalence [14]. The datasets for the years including 2012–2016 were included, which spans the period of time between 1 January 2012 and 31 December 2016.

Study population

All patients within the database with an International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9 and ICD-10 CM), all diagnostic codes for hereditary hemochromatosis (275.01 and E83.110) were included in our study, and were compared to all other discharges that did not have an associated ICD-9 CM diagnostic code for hereditary hemochromatosis. Of this population, patients who underwent spinal fusion were identified using the respective ICD-9 and ICD-10 CM procedural codes (81.0-9, 81.30-9, 0RG0-2,4,6-8xxx, 0RGAxxx, 0SG0,1,3,5-8xxx). Patients with secondary causes of iron overload (e.g., repeated transfusion therapy) were excluded from the study.

Variable definition

Extracted data were divided into patient and hospital characteristics. Patient characteristics included age, sex, ethnicity, median household income in zip code, Charlson Comorbidity Index, and weekend admission. Hospital characteristics included, teaching status, hospital bed size, and location.

Each patient's vital status at discharge, length of hospital stay, and total hospitalization charges were also obtained from the NIS. To enable adjustment for patient comorbidities, the Deyo adaptation of the Charlson Comorbidity Index was used, which has been validated for large database analysis [15].

Outcomes

The primary outcome of our study was to determine the use of spinal fusion in the hereditary hemochromatosis population when compared to the general nonhereditary hemochromatosis population. Secondary outcomes were resource utilization, measured by hospital LOS, total hospitalization charges, and hospital costs. Total hospital charges represent the amount of monetary resources that each hospital billed to insurance companies for each case, while hospital costs represent the amount of monetary resources invested by each institution in providing patient care. Hospital costs were calculated by multiplying the cost-to-charge ratios for the respective institutions with the total hospitalization charges. Cost-to-charge ratios are provided by the HCUP on each discharge in the database to enable this calculation. Because multiple years of data were utilized, all costs and charges were adjusted for inflation to convert them into 2016 $USD.

Statistical analysis

Discharge-level weights within the NIS were used to estimate the total number of patients who had hereditary hemochromatosis and underwent spinal fusion surgery [13]. The Fisher exact test was used to compare proportions, and the Student *t* test was used to compare means. Propensity scores were used to match patients with spinal fusion and hereditary hemochromatosis to those who underwent spinal fusion with no hereditary hemochromatosis. A nonparsimonious multivariate logistic regression model was developed to estimate the propensity of associated hereditary hemochromatosis using age, gender, ethnicity, median income in patient's zip code, Charlson Comorbidity index, location, and number of beds as covariates. The probability of having associated hereditary hemochromatosis was used as the propensity score, and a greedy matching algorithm was used to find the best matches for each patient with spinal fusion with a caliper distance of 0.01. To assess associations between hereditary hemochromatosis and the various outcomes of interest, multivariable conditional logistic regression models were built with each factor as the dependent variable (outcome) and hereditary hemochromatosis as the predictor in addition to insurance carrier, hospital teaching status, and weekend admission as additional covariates. All statistical analyses were conducted using STATA, Version 14 (StataCorp LP, College Station, Texas, USA).

Results

Patients and hospital characteristics

Out of a total of 97 510 patients with hereditary hemochromatosis that were admitted in the documented study period, a total of 39 780 patients with hereditary hemochromatosis were identified and propensity matched to nonhereditary hemochromatosis controls. The mean age of patients with hereditary hemochromatosis undergoing spinal surgery was 61 years, and 65% were females. The majority of patients were Caucasian (93.3%), followed by Hispanic (3.3%), African American (2.0%), Asian (0.7%), and Native American (0.7%). The hereditary hemochromatosis cohort was older, had lower income percentiles, and was more likely to have Medicare insurance and less likely to have Medicaid or self-pay. There was no significant difference in the two patient cohorts in terms of sex, ethnicity, or Charlson Comorbidity Index. The two cohorts also differed in terms of hospital location and hospital bed size. A significantly higher number of patients in the hereditary hemochromatosis cohort were treated at a urban hospital (97.5%), compared to the non-hereditary hemochromatosis cohort (2.5%) ($P = 0.02$). Patients in the hereditary hemochromatosis cohort were also more likely

to be admitted to a large hospital compared to patients without hereditary hemochromatosis. The teaching status of the hospital did not differ between the two patient cohorts. Table 1 displays the values and significance levels between both cohorts.

Primary outcome

Patients with hereditary hemochromatosis underwent significantly more spinal fusion surgery (0.7%) compared to patients without hereditary hemochromatosis (0.3%) ($P < 0.01$). This was confirmed after adjusting for confounders, as patients with hereditary hemochromatosis displayed an adjusted odds ratio of undergoing spinal fusion of 2.13 compared to patients without hereditary hemochromatosis ($P = 0.05$). In addition, 2.0% of patients in the hereditary hemochromatosis cohort underwent spinal surgery compared to 1.5% of patients in the nonhereditary hemochromatosis cohort. However, this difference did not reach statistical significance ($P = 0.16$). When substratified by the type of spinal surgery other than spinal fusion, the odds did not differ significantly between the cohorts. All outcomes are displayed in Tables 2 and 3.

Hospital length of stay

The mean LOS in patients with hereditary hemochromatosis undergoing spinal surgery was 3.6 days compared to 3.2 days in patients without hereditary hemochromatosis undergoing spinal surgery. Although patients with hereditary hemochromatosis had longer mean LOS compared to nonhereditary hemochromatosis patients, this was not significantly different ($P = 0.31$). Mean LOS along with additional LOS is depicted in Table 4.

Table 2. Crude percentages of patients with and without hereditary hemochromatosis undergoing various types of spinal surgeries along with the associated *P* values

Variable	No hereditary hemochromatosis (%) (*N* = 2 939 720)	Hereditary hemochromatosis (%) (*N* = 39 780)	*P* value
Spinal surgery (*N* = 2 979 500)	1.5	2.0	0.16
Fusion (*N* = 1 008 561)	0.3	0.7	<0.01
Vertebroplasty (*N* = 153 444)	0.1	0.1	0.10
Vertebral insertion (*N* = 502 344)	0.3	0.4	0.28
Vertebral excision (*N* = 1 315 151)	0.9	0.8	0.9

Table 3. Adjusted odds ratio of spinal surgery stratified by subtype in patients with hereditary hemochromatosis compared to patients with no hereditary hemochromatosis

Variable	aOR	95% CI	*P* value
Spine surgery (any type)	1.06	0.68–1.67	0.27
Fusion	2.13	1.01–4.51	0.05
Vertebroplasty	1.32	0.30–5.77	0.72
Vertebral Insertion	0.84	0.23–3.08	0.79
Vertebral Excision	0.76	0.39–1.49	0.43

aOR, adjusted odds ratio; CI, confidence interval.

Table 1. Baseline patient and hospital characteristics of patients with and without hereditary hemochromatosis after propensity-score matching

Variable	No hereditary hemochromatosis (*N* = 39 800)	Hereditary hemochromatosis (*N* = 39 780)	*P* value
Mean age (years [SD])	56.3 [14.9]	60.7 [11.9]	<0.01
Female	68.3% (27 183)	65% (25 857)	0.68
Ethnicity			
Caucasian	90% (35 820)	93.3% (37 115)	
African American	2.5% (995)	2.0% (796)	0.45
Hispanic	7.5% (2985)	3.3% (1313)	
Asian	0.0% (0)	0.7% (280)	
Native	0.0% (0)	0.7% (276)	
Income (median)			
1 (0–25th percentile)	5.9% (2348)	19.1% (7588)	
2 (26–50th percentile	16.8% (6686)	22.3% (8881)	
3 (51–75th percentile)	26.0% (10 348)	30.6% (12 178)	0.02
4 (76–100th percentile)	51.3% (20 418)	28.0% (11 143)	
Insurance			
1 Medicare	35.8% (14 248)	41.9% (16 668)	
2 Medicaid	8.3% (3303)	4.4% (1750)	
3 Private insurance	46.7% (18 587)	45.6% (18 140)	0.03
4 Self-pay	1.7% (677)	0.6% (239)	
5 No charge	0.0% (0)	0.0% (0)	
6 Other	7.5% (2985)	7.5% (2983)	
Charlson			
0	68.3% (27 183)	60.6% (24 107)	0.36
1–2	27.5% (10 945)	36.3% (14 440)	
3>	4.2% (1672)	3.1% (1233)	
Weekend admission	2.5% (995)	4.4% (1750)	0.35
Hospital location			
Rural	15.8% (6288)	2.5% (997)	0.015
Urban	84.2% (33 512)	97.5% (38 783)	
Teaching status			
Nonteaching	42.5% (16 915)	34.4% (13 684)	
Teaching	57.5% (22 885)	65.6% (26 096)	0.66
Bed size			
Small	44.2% (17 590)	24.4% (9706)	
Medium	49.2% (19 580)	23.7% (9428)	0.01
Large	6.6% (2630)	51.9% (20 646)	

Table 4. Mean expenditures and mean hospital length of stay of patients with and without hereditary hemochromatosis undergoing spinal surgery

Variable	No hereditary hemochromatosis	Hereditary hemochromatosis	Mean difference	*P* value
Mean total hospitalization costs	$24 588	$26 317	$1729	0.43
Mean total hospitalization charges	$49 496	$100 303	$50 087	<0.01
Mean hospital length of stay (days)	3.2	3.6	0.4	0.31

Total hospitalization costs and charges

The mean hospital cost for patients with hereditary hemochromatosis undergoing spinal surgery was $26 317, while the mean hospital cost for patients without hereditary hemochromatosis undergoing spinal surgery was $24 588. This was not a statistically significant difference ($P = 0.43$). The mean total hospitalization charges did differ significantly between patients with hereditary hemochromatosis with their mean total hospitalization charges being $100 303, compared to $49 496 in patients without hereditary hemochromatosis undergoing spinal surgery ($P < 0.01$). Mean total hospitalization costs and charges can be seen in Table 4.

Discussion

The current study is the first to demonstrate that patients with hereditary hemochromatosis have increased odds of undergoing spinal fusion compared to patients without hereditary hemochromatosis using the NIS database. In addition, this study is also the first to examine LOS, and expenditures related to spinal surgery in patients with hereditary hemochromatosis. Our study showed that patients with hereditary hemochromatosis who undergo spinal surgery have a significantly increased mean total hospitalization charges than patients without hereditary hemochromatosis. Our cohorts were matched by propensity scores, and differed only as expected with patients with hereditary hemochromatosis being treated at larger, urban hospitals which is typical of patients with a complex disease process such as hereditary hemochromatosis.

There are currently no other large studies which examine the impact of spinal arthropathy in patients with hereditary hemochromatosis. Furthermore, there is no data on the need for spinal surgery or the relationship between spinal arthropathy and the need for spinal surgery, in particular spinal fusion in this patient population. Studies which specifically delve into the prevalence of spinal arthropathy in patients with hereditary hemochromatosis are also lacking, yet Valenti *et al*. [16] in 2008 examined 88 patients with hereditary hemochromatosis, and found 34% to have radiographic evidence of spinal arthropathy based on radiograph of the lumbar spine, while Bywaters *et al*. [4] found a prevalence of spinal arthropathy in seven of 47 patients (15%). However, prior studies have only examined the etiopathogenesis of spinal arthropathy in hereditary hemochromatosis, which could explain the presence of spinal arthropathy in this patient population [1,5,17–22]. Thus, it is more helpful to examine the prior literature in regards to etiologies of spinal arthropathy, which include a hereditary hemochromatosis-associated arthritis that can mimic osteoarthritis or inflammatory arthritis, osteoporosis related to iron overload inducing hypopituarism and subsequent hypogonadism, and hereditary hemochromatosis-associated CPPD.

First, it is clear that hereditary hemochromatosis is associated with a chronic progressive arthropathy which may be an intermediate phenomenon between osteoarthritis and RA. In fact, it is difficult to distinguish whether patients with hereditary hemochromatosis who present with arthropathy have osteoarthritis or hereditary hemochromatosis-associated joint changes. Radiographically on radiograph, arthropathy associated with hereditary hemochromatosis is similar to osteoarthritis with subchondral stenosis and joint space narrowing, but patients with hereditary hemochromatosis tend to have associated subchondral lucencies and chondrocalcinosis [1]. There are data that MRI can help distinguish between the two entities, but these studies mainly focus on arthropathy related to the hands rather than the spine [23]. However, synovial tissue analysis during joint replacements in patients with hereditary hemochromatosis has shown a distinct infiltration of macrophages and neutrophils which is absent in osteoarthritis, and a lack of B cells, and T cells seen in RA [24]. Thus, it is clear that there is a distinct entity of osteoarthritis-like arthritis which is associated with hereditary hemochromatosis, yet it is hard to clinically distinguish between other types of arthritis using imaging.

This arthropathy is not improved by phlebotomy, and it is independent of the ferritin level [1,7,10]. One theory is that the human homeostatic iron regulator protein (HFE) mutation may be arthritogenic, which would support a mechanism independent of hepcidin and iron that may explain why arthropathy is not improved by phlebotomy [18,22]. This is supported further by the fact that Sandhu *et al*. [22] found a higher prevalence of arthropathy in patients with HFE-associated hereditary hemochromatosis compared to non-HFE-associated hereditary hemochromatosis, even when adjusting for serum iron levels.

Next, spinal arthropathy and the increased rates of spinal fusion could be secondary to hypopituitarism-related hypogonadism leading to increased rates of osteoporosis in patients with hereditary hemochromatosis [25]. As expected, this phenomenon is improved with iron regulation via phlebotomy as the mechanism is driven by iron overload damaging the pituitary gland [25,26]. Finally, hereditary hemochromatosis is clearly associated with CPPD, and this is associated with spinal arthropathy typically seen in the cervical and lumbar spine, rather than the thoracic spine [1,20,21,27]. CPPD is seen radiographically with the presence of chondrocalcinosis. It is linked to disease chronicity in hereditary hemochromatosis as it is a late manifestation, and its prevalence has been shown to be 5–49% [1]. There are two proposed mechanisms for the association between hereditary hemochromatosis and CPPD. First, iron has an inhibitory effect on pyrophosphatases. Second, hereditary hemochromatosis is associated with increased serum levels of midregion parathyroid hormone fragments containing the amino acids 44–68 which have been implicated in the development of CPPD [19,21]. Unlike osteoporosis in patients with hereditary

hemochromatosis that is improved by phlebotomy, CPPD is not improved by phlebotomy [7].

The current study shows that patients with hereditary hemochromatosis have a higher inpatient prevalence of undergoing spinal fusion compared to patients without hereditary hemochromatosis, even after adjusting for age. Indications for spinal fusion are typically radicular pain from conditions including disc herniation or spinal stenosis, as well as nonspecific low back pain secondary to degenerative changes that are not amenable to conservative therapy.

The increased odds of undergoing spinal fusion with hereditary hemochromatosis are likely explained by the presence of spinal arthropathy seen in this patient population. The literature has shown that, unlike other clinical manifestations of hereditary hemochromatosis that are improved by phlebotomy, the hereditary hemochromatosis-associated arthritis and CPPD (both which can contribute to spinal arthropathy) are not improved by phlebotomy. Thus, one could speculate that while the life expectancy of patients in hereditary hemochromatosis has improved with regular phlebotomy and liver transplantation, patients are developing more complications of arthropathy [28,29].

While total hospitalization costs did not differ significantly in patients with and without hereditary hemochromatosis undergoing spinal surgery, hospitalization charges were markedly increased in patients with hereditary hemochromatosis. This is suspected to be secondary to changing insurance policies and models.

In terms of clinical relevance, spinal arthropathy is a potentially underdiagnosed complication of patients with hereditary hemochromatosis. Its implications on the patient as well as healthcare resources have also likely been underestimated as shown by the increased rates of spinal fusion in this patient population. It is important for clinicians to determine the overall impact and prevalence of spinal arthropathy in this community, as current treatment with phlebotomy fails to adequately control or prevent spinal complications. It is unknown whether earlier diagnosis or more stringent management could prevent patients from undergoing spinal fusion. Patients may also need to be educated that spinal arthropathy is a hereditary hemochromatosis-related complication.

The major strength of this study was the large patient volume which is made possible by utilizing NIS which is the largest US nationwide inpatient database. Prior studies examining hemochromatosis and in particular, the association with arthropathy has lacked large patient numbers. In addition, another strength is the fact that it is based on recent data which accurately reflects the patient population's burden of joint disease assuming that the majority of patients received iron regulating therapy with phlebotomy, compared to older studies prior to the advent of therapy.

Several limitations do need to be acknowledged. First, this study utilizes the NIS database, which is solely an inpatient database, meaning that patients represented are patients manifesting with disease who require a hospital admission, for which there may be a significant selection bias. In addition, due to the administrative nature of the database, it has been documented that claims-based databases are susceptible to inaccurately entered or missing codes [30]. It is also not possible to track individual patients in an effort to see if they received guideline-directed medical therapy including regular phlebotomy, iron chelation, or treatment of liver fibrosis or cirrhosis if present, or if the same patient was readmitted for any given reason. Furthermore, the specific indication for spinal fusion surgery is not able to be determined from the dataset. It is speculated that the increased inpatient prevalence of spinal fusion was secondary to spinal arthropathy, but there is no way to confirm this using NIS. For example, these patients could have underwent spinal fusion for another indication such as trauma or tumor compression. Thus, in order to confirm that the increased use of spinal fusion in the hereditary hemochromatosis patient community is secondary to spinal arthropathy leading to nonspecific back pain, one would have to repeat the retrospective study using a more comprehensive patient database with the ability to track indication for spinal fusion. Long-term outcomes following spinal fusion surgery such as readmission rates or symptomatic relief can also not be determined by using NIS. Medication use and laboratory data are not available from the dataset, and costs and charges are limited to inpatient only.

Conclusion

Our current study brings spinal arthropathy to the forefront of hereditary hemochromatosis, as this is the first study to reveal that patients with hereditary hemochromatosis have approximately twice the inpatient use of spinal fusion as compared to the general population. This is likely secondary to nonspecific lower back pain secondary to spinal arthropathy requiring spinal fusion. While the mortality of hereditary hemochromatosis is improved by phlebotomy, arthropathy is becoming one of the major complications, and there are currently no therapies to prevent this joint disease.

Future studies are needed to explore the effectiveness of spinal fusion in treating spinal arthropathy related to hereditary hemochromatosis. In addition, future studies are needed to better determine the prevalence of spinal arthropathy in patients with hereditary hemochromatosis, and potential therapies other than phlebotomy which could potentially prevent the formation of arthropathy. It is still unknown whether increased screening and earlier diagnosis of hereditary hemochromatosis with a focus on early iron regulation could prevent the development of arthritis or CPPD. Finally, it is important that additional studies continue to shed light on the economic burden secondary to hereditary hemochromatosis in an effort to find a cost-effective treatment strategy.

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This manuscript is not under consideration for publication elsewhere, and the publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that if accepted, it will not be published elsewhere in the same form, in English or any other language, including electronically without the written consent of the copyright-holder.

Conflicts of interest

There are no conflicts of interest.

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