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Impact of Hereditary Pancreatitis on Patients and their Families

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Abstract

Hereditary pancreatitis (HP), a highly penetrant (~80%) autosomal dominant disease associated with *PRSS1* variants, causes acute pancreatitis (AP) in childhood and chronic pancreatitis (CP) by early adulthood. Other clinical features include pain, diabetes and risk of pancreatic cancer. HP kindreds were prospectively recruited from 1995–2015. At enrollment, study participants completed medical and family history questionnaires, and provided samples for genotyping. Participants were re-contacted between 2015–2017 and asked to complete a survey on concerns and experiences related to HP, *PRSS1* testing and genetic counseling. Data were analyzed with descriptive and thematic methods. 39 affected participants with HP and 21 unaffected family members completed the survey. Among unaffected family members, 'worry' and 'helplessness' were frequently described as the most difficult problem in their family because of HP, particularly with regard to pain. Three participants described the impact of drug addiction on their family. 'School or work limitations' was the leading financial concern, with 65.5% (36/55) rating it as 'moderately' or 'extremely important'. Unexpectedly, only 62% (21/34) of affected *PRSS1* carriers believed the chance for a parent to pass HP to his or her children was 50%, whereas 18%

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Authorship Contributions

C Shelton contributed to study design, data collection, analysis and interpretation of data, drafting of manuscript and critical revision of the manuscript for important intellectual content. R Grubs contributed to study design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. C Umapathy contributed to data collection and critical revision of the manuscript for important intellectual content. D Yadav contributed to study concept and design, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. D Whitcomb contributed to study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding and study supervision. All authors approve the final draft submitted.

Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study.

Animal Studies

No non-human animal studies were carried out by the authors for this article

Conflicts of Interest

DCW serves as a consultant for AbbVie, Regeneron and Ariel Precision Medicine and has equity in Ariel Precision Medicine. CA Shelton, RE Grubs, C Umpathy and D Yadav declare that they have no conflict of interest.

(6/34) believed the chance was 100%. The impact of HP on individuals and families varied, which may reflect the highly unpredictable nature of HP severity and outcomes. Based on current and previously reported findings, an overview of important issues for genetic counselors to consider for counseling HP families is included.

Keywords

Hereditary pancreatitis; PRSS1; Thematic analysis; Family perspectives; Genetic counseling; Family; Psychosocial; Risk Perception

Introduction

Hereditary pancreatitis (HP) is a rare, autosomal dominant inflammatory disorder of the pancreas, typically caused by gain-of-function mutations in cationic trypsinogen (*PRSS1*). HP is characterized by the onset of acute pancreatitis in childhood, with progression to chronic pancreatitis by early adulthood. Not all *PRSS1* carriers develop clinical disease, and the penetrance has been estimated to be 80% (Amann, Gates, Aston, Pandya, & Whitcomb, 2001; Howes et al., 2004; Shelton, Umapathy, Stello, Yadav, & Whitcomb, 2018; Sibert, 1978; Sossenheimer et al., 1997).

Clinical presentation, progression and severity of HP are highly variable among patients and families. Abdominal pain is difficult to manage and has significant implications for physical and mental quality of life (Amann et al., 2013; Machicado et al., 2017). Carriers are at risk to develop diabetes mellitus, exocrine pancreatic insufficiency, and pancreatic cancer (Howes et al., 2004; Joergensen, Brusgaard, Cruger, Gerdes, & Schaffalitzky de Muckadell, 2010; Lowenfels et al., 1997; Rebours et al., 2009; Shelton et al., 2018).

Although the genetic etiology of HP was identified in 1996 (Gorry et al., 1997; Whitcomb, Gorry, et al., 1996; Whitcomb, Preston, et al., 1996), little is known regarding the psychosocial implications of HP on both patients and their families. Guidelines for genetic testing and counseling were established in 2001, but few studies have evaluated patient experiences with testing and counseling (Ellis, 2004; Ellis, Lerch, Whitcomb, & Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, 2001). In one previous study, *Applebaum, et al.* (2001) found that individuals with HP were motivated to participate in research to help family members and future generations (Applebaum-Shapiro, Peters, O'Connell, Aston, & Whitcomb, 2001). Moreover, participants were most commonly motivated to pursue genetic testing due to the 'disturbing nature of seeing relatives affected with hereditary pancreatitis' (Applebaum-Shapiro, Peters, et al., 2001). Insights from this study helped inform genetic counseling guidelines and information for patients (Ellis, 2004). Genetic diseases affect entire families and are frequently accompanied by a number of psychosocial implications, including anxiety, depression, grief and worry (Eijzenga, Hahn, Aaronson, Kluijt, & Bleiker, 2014; McAllister et al., 2007). Furthermore, counseling considerations for HP must span from counseling for a highly penetrant childhood onset disease to a predisposition for pancreatic cancer in adulthood. Therefore, identifying and addressing concerns and familial implications are important to ensure effective care and counseling interventions.

Although these features make HP a unique genetic disorder, comparisons can be made to another genetic disease for which individuals also experience severe pain crises – sickle cell disease (SCD). As with a pancreatic attack, a sickle cell vaso-occlusive pain crisis requires aggressive analgesic management in the hospital (Yawn et al., 2014). Frequently observed comorbidities of SCD include depression, anxiety and reduced quality of life (Graves, Hodge, & Jacob, 2016; Pecker & Darbari, 2019). Furthermore, the financial impact of SCD is significant, particularly due to hospitalizations (Kauf, Coates, Huazhi, Mody-Patel, & Hartzema, 2009). SCD places significant financial and psychosocial strain on caregivers, and has important implications for family functioning (Brandow, Brousseau, & Panepinto, 2009; Gold, Treadwell, Weissman, & Vichinsky, 2011; Keane & Defoe, 2016). The impact of SCD is multidimensional, and includes negative effects on physical, psychosocial and occupational well-being (Thomas & Taylor, 2002). As another disease in which individuals experience severe pain attacks requiring frequent hospitalization, HP may have a similar psychosocial and financial impact on affected individuals and their family members.

The current study extends previous studies on HP by investigating the impact of HP on patients and family members on mental health, relationships and concerns. Guided by known implications of SCD, in which pain crises have well-studied psychosocial effects on families, a survey was created to examine these issues in individuals with HP and their family members. The exploration of these issues is relevant for both genetic counseling approaches and effective patient management.

Methods

The HP Study

The HP Study at the University of Pittsburgh (ClinicalTrials.gov Identifier: NCT00004475) began recruiting participants in 1995 to describe the clinical characteristics of HP, evaluate suspected HP kindreds, and obtain biological samples. Affected individuals and their family members were consented under an IRB-approved protocol (Applebaum-Shapiro, Finch, et al., 2001). Study participants completed structured case report forms and minimum three-generation pedigrees were constructed as previously described (Applebaum-Shapiro, Finch, et al., 2001; Shelton et al., 2018). Available medical records were reviewed by a licensed physician (CU), and HP was determined by 1) a personal history of pancreatitis with an identified *PRSS1* mutation, or 2) according to clinical criteria (≥ 2 individuals with pancreatitis in ≥ 2 generations) and the absence of other explanatory etiologies (e.g. alcohol).

Blood was collected, and DNA was extracted and assessed for six known pathogenic *PRSS1* variants (p.R122H, p.N29I, p.R122C, p.K23R, p.A16V, p.R116C) with Sanger sequence verification. When available, results were confirmed with clinical test reports. For a limited number of participants, DNA was not provided or was of suboptimal quality. For these participants, *PRSS1* status was determined by clinical test reports (n=3) or obligate status (n=4). For one affected individual in an established *PRSS1* kindred, neither DNA nor a clinical genetic test report were provided. However, positive *PRSS1* genetic test results were available for close family members, and the participant reported a positive *PRSS1* status

from clinical genetic testing, which was consistent with the known familial *PRSS1* genotype.

Study Participant Re-ascertainment

At the original time of their enrollment, study participants consented to be recontacted in the future for follow-up. In 2015, previous study participants over the age of 18 years, including unaffected family members, were requested to reconsent to continue their participation in the HP Study via an advertisement in a biannual pancreas research newsletter produced by the Division of Gastroenterology, University of Pittsburgh. This newsletter is distributed to participants in the HP Study, as well as participants in other pancreatic disease studies at the University of Pittsburgh. The first issue was distributed in 2004.

Study participants from known *PRSS1* HP families (71 families comprised of 183 known adult *PRSS1* carriers) were further targeted for follow-up by phone a minimum of 2 times. If participants could not be reached by phone, then they were sent email and mail invitations to participate in the new survey. When participant contact information was outdated, other participants in the family were asked to invite their family members to contact the study office. Due to outdated contact information, only a limited subset of participants could be contacted during this phase of the study. Study participants who re-consented to participate signed an addendum consent form to participate in a new survey on concerns and experiences related to HP, *PRSS1* testing and genetic counseling. Consented participants were sent the IRB-approved survey by mail (paper copy) or email (an individual web link to complete the survey online using Qualtrics software), according to individual preference.

Instrumentation

A survey to assess mental health, financial and general concerns regarding HP, and experiences with genetic testing and genetic counseling was created using new and existing instruments. All participants (both affected and unaffected) were asked to provide an update to their medical history, alcohol and tobacco exposure, height, and weight using standardized case report forms (Whitcomb et al., 2008). Collected medical history included a standardized case report form on pancreatic disease, pain and related symptoms. This information was used to determine changes in health status, such as disease penetrance in a previous unaffected *PRSS1* carrier. Anxiety and depression were measured using the Patient Reported Outcomes Measurement Information System (PROMIS®) short forms 1.0 Anxiety 4a and Depression 4a. Questions on concerns, perspectives and experiences were divided into three sections (General and Financial Concerns Regarding HP, Genetic Testing, and Genetic Counseling), which included Likert scales, rank order items and open-ended questions (Supplementary Table 1). In the first section, study participants were asked to provide short answer responses to: '*What is the most difficult problem for you to deal with because of hereditary pancreatitis in you or your family?'* and subsequently, '*Why is the problem noted in the previous question the most important problem?'* In the last section, participants were asked to answer the following short answer questions regarding genetic counseling: '*Please describe the most useful aspects, if any, of your experience speaking with a genetic counselor.*' and '*Please describe the information, if any, that you think should*

be provided by a genetic counselor.' Both affected and unaffected participants were asked to answer each question.

Data Analysis

Baseline characteristics were compared between groups using the χ^2 test or Fisher's exact test for categorical data, or Kruskal-Wallis for continuous data. The HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice) was used to score the PROMIS® instruments (Anxiety 4a, Depression 4) (Schalet et al., 2016). Kruskal-Wallis tests were used to compare anxiety and depression scores between affected and unaffected participants. The results of Likert scale, rank-order and multiple-choice questions are reported as counts and percentages for affected and unaffected participants. For simplicity, 5-level Likert responses were summarized into 3 categories as applicable – e.g. 'not at all important', 'slightly/somewhat important', and 'moderately/extremely important'.

Short responses to open-ended questions were subjected to a limited inductive thematic analysis when possible. Responses were reviewed twice, after which initial data-driven codes were generated across the dataset. Codes were grouped into possible themes, as described by Braun and Clarke (2006). Coding was conducted by the lead author and reviewed by a second author (REG). Differing opinions on the codes and emerging themes were examined and resolved. An iterative process of reviewing the data and codes as well as refining the themes was conducted, during which revisions were made to the thematic map to accurately reflect the dataset. Additional short answer questions that lacked sufficient depth for thematic methods were reviewed for content.

Results

Study Participants

39 affected participants with HP and 21 unaffected family participants completed the survey, for a total of 60 subjects. 7/21 unaffected family participants were identified to be asymptomatic carriers of a *PRSS1* mutation. Of the 39 individuals with clinical disease, 34 had a confirmed *PRSS1* mutation (+ 1 reported *PRSS1* mutation). 26 families were represented by study participants: 22 families with a *PRSS1* mutation (19 *PRSS1* p.R122H and 3 *PRSS1* p.N29I) and 4 families that met clinical criteria without an identified *PRSS1* mutation. The mean number of participants per family was 2.3 (IQR 1 – 3.75).

Participant demographics and characteristics are presented in Table 1. Of the individuals who reported their ancestry, all were European. No significant differences between affected and unaffected participants were identified for sex, age, BMI, or familial *PRSS1* mutation. Smoking status and ever drinker status were nearly significant (p=0.13 and 0.06) with a greater proportion of unaffected particpants reporting exposure to alcohol and cigarettes compared to affected participants.

Anxiety and Depression

T-scores from the Anxiety 4a, Depression 4a, and Global Health PROMIS® short forms were compared between affected and unaffected participants. There was an observation of

lower anxiety scores in affected individuals with HP compared to unaffected participants (45.6± 7.8 v. 49.4v±9.3, p = 0.08). Depression scores were significantly lower in affected participants compared to unaffected participants (44±5.3 v. 49±4.3, p = 0.02). Although an observation of higher anxiety and depression in unaffected participants was identified, scores were similar to the general population (mean 50, standard deviation 10).

Financial Concerns

All study participants were asked to rate the level of importance of four financial concerns from 'Not at all important' to 'Extremely important'. A similar distribution of responses was seen across affected and unaffected participants. 'School or work limitations' was found to be the most important financial concern, with 65.5% (36/55) participants rating it as 'moderately/extremely important' (Table 2).

Reasons to Pursue Genetic Testing

Of the participants in the study, 83% (30/36) of affected participants and 45% (9/20) of unaffected participants indicated that they had received genetic testing for *PRSS1*-hereditary pancreatitis and were told the results. Participants were then asked to select the most important reason they pursued genetic testing. Of the 15 individuals who answered this question and chose only a single answer, 40% (6/15) selected that they pursued genetic testing 'to help others through research' (Supplementary Table 2). Interestingly, one participant indicated that the most important reason was 'the disturbing emotions prompted by witnessing a relative afflicted with HP'.

Study participants were asked to rate their agreement with reasons to pursue genetic testing on a 5-level Likert scale from 'Strongly disagree' to 'Strongly agree'. Participants agreed with six of seven reasons presented in Table 3. Responses to 'pressure from relatives' was varied across both affected and unaffected participants. 'Help[ing] others through research' and 'Help[ing] one's future generations' were the most strongly agreed upon reasons to pursue genetic testing in both affected and unaffected participants. Although responses to 'The disturbing emotions prompted by witnessing a relative afflicted with HP' were varied across affected participants, the majority (90%, 18/20) of unaffected participants agreed with this reason.

Perceived risk to pass HP to children

Participants were asked to select what they believed the chance to pass HP to offspring was from four choices: '25% (1 in 4)', '50% (1 in 2)', '100%' and 'Unknown'. 57% of the participants identified that the chance was 50% (1 in 2). Of affected individuals with a known *PRSS1* mutation for autosomal dominant HP, 62% (21/34) correctly identified that the chance was 50% (1 in 2), while 18% (6/34) identified that the risk to offspring was 100%. Data on the time elapsed between counseling and recall were not collected.

Genetic Counseling

Ten study participants completed the first short answer question in the Genetic Counseling section ('*Please describe the most useful aspects, if any, of your experience speaking with a genetic counselor*'), nine of which described the information provided by the genetic

counselor, i.e. the 'content' of the session. Participants described the usefulness of receiving information on new research findings and research opportunities, being provided with an explanation of the genetic testing process and receiving results, and education on chance of transmission and future planning, natural history, and disease management (Supplementary Table 3). One participant described counselor behavior, specifically receiving empathy and advocacy.

Twenty-four participants completed the second question ('*Please describe the information, if any, that you think should be provided by a genetic counselor*'). Answers covered major topics of information that study participants believe should be provided by a genetic counselor, including inheritance, disease natural history, treatment and management strategies, resources, information regarding genetic testing, new research findings, and family planning (Table 4). In addition, information on lifestyle modifications and other strategies to minimize pancreatic attacks was noted by participants. One individual specifically stated that clients should be made aware of the mental health implications of HP.

Most Difficult Problems due to HP

Twenty-four answers to '*What is the most difficult problem for you to deal with because of hereditary pancreatitis in you or your family?*', though generally short, were subjected to a limited inductive thematic analysis. The purpose of this analysis was to identify issues that healthcare professionals should be aware of, and which may be appropriate to identify and address during counseling. The analysis identfied three main themes: Worry, Quality of Life and Impact on family. A number of responses were found to address more than one theme. One response was not coded into one of these themes and is discussed in an 'other' category. The majority of themes and their subthemes were recognized to be a direct or indirect consequence of pain.

Worry—Both affected and unaffected participants worried about other family members. A feeling of helplessness to ease the suffering of affected family members was described by unaffected individuals and symptomatic participants, alike. The following quotes illustrate the worry expressed by several participants:

> "I feel helpless when I see my siblings suffering when they have a painful attack. I can fill the void in their day to day routines, but there is nothing I can do to ease their pain or prevent future spells." Participant 031, unaffected
>
> "…Let's just say it's (pancreas) not my favorite organ."
>
> (Response to subsequent *Why* question)
>
> "It has been dificult to watch loved ones suffer so severely." Participant 051, affected
>
> "The pain before I had a sphincterotomy. Difficult to see my son, now near death, suffer along with my daughter and grandson and grandaughters."
>
> (Response to subsequent *Why* question)

"Appears to be no cure or pain relief for their pancreatitis." Participant 016, affected

Concern was described in relation to younger generations. An older participant with chronic disease worried about her family members rather than herself. She responded:

> "I'm concerned about my kids and grandkids."
>
> (Response to subsequent *Why* question)
>
> "Because I'm 90 years old. But it's them that has a life ahead of them." Participant 036, affected

Affected participants worried about when a pain attack might occur and about finances or health insurance. For example, one participant described her most difficult problem:

> "Uncertainty of when and if an attack (episode) might occur."
>
> (Response to subsequent *Why* question)
>
> "Need to have pain meds available if needed." Participant 049, affected

Quality of Life—The effect of HP on health-related quality of life, particularly activities of living and psychoscocial wellbeing, was also described. One individual responded as follows.

> "Pain-lack of sleep; Expensive medications – my sister has no insurance, creon - $500/month; Insurance-fear of preexisting condition if obamacare defeated."
>
> (Response to subsequent *Why* question)
>
> "They prevent me from living my life-working-fini[s]hing my PhD or doctorate in this field. I have many post masters hours. I want to help others." Participant 017, affected

Another individual expressed the impact of HP on his grandchildren:

> "I hate to see my children or grandchildren in pain."
>
> (Response to subsequent *Why* question)
>
> "Pain effects their school, activities of daily living, happiness." Participant 048, unaffected

Impact on Family—Participant responses suggested an impact of HP on family dynamics and structure. More specifically, unaffected family members commented on loss of loved ones, the impact of drug addiction, and changes to family relationships and roles. Loss within the family was mentioned and seemed to be tied with worry about other family members:

> "Loss of my sister and father, as well as aunts and cousins to this disease. Also very difficult to witness what the disease has done to other siblings and their children - pain, loss of quality of life, addiction to pain meds."
>
> (Response to subsequent *Why* question)

> "Loss of my sister, who was my best friend, at such an early age. Watching her 3 young children grow up without their mom." Participant 034, unaffected

Addiction was also reported by a number of participants. Participants describe the formation of addiction during pain management:

> "My father had pancreatitis, and he was in and out of the hospital due to pain or other issues. The pain management he sought out for ended up leading to addiction to those same pain medicines which in turn lead to harder addictions which eventually killed him." Participant 001, unaffected

> "Seeing family suffer. My younger brother … passed away … due to drug addiction after years of struggling. He had HP and couldn't stop after hospital stays."
>
> (Response to subsequent *Why* question)
>
> "Lost a brother. I have watched brothers, cousins, nieces and more suffer for years." Participant 008, unaffected

Both drug addiction and loss appeared to have a significant impact on family structure, relationships and roles, as seen in the responses above. One participant described the impact of her father's disease on her life:

> "My father being disabled from the disease i[s] the most important problem because it hindered having a deep relationship with m[y] father. It impacted and shaped my entire life." Participant 055, unaffected

Other—In addition to the above themes, one participant gave a particularly poignant response regarding her experiences receiving medical care for chronic HP:

> "The most difficult is Doctors understanding, and listening to me, misdiagnose me all the time. They will not listen when I tell them that certain meds can bring on an attack, that I do not drink, and that I am not a diabetic that sometimes stress can bring on an attack that I need help with the pain that I am in at times I can handle a pain level of 6 – 7 but when it gets higher than that I need help. That I know what to do in an attack, I have had so many of them I have lost count on how many I have had."
>
> (Response to subsequent *Why* question)
>
> "I have no Doctor at this time, the last one told me that I was on my own." Participant 043, affected

Discussion

Hereditary pancreatitis is a debilitating disease with high morbidity and significant impact on families. In this study, 60 participants rated the importance of financial concerns and provided opinions on genetic counseling and statements on difficulties that affect HP patients and their unaffected family members. Although significant differences were not identified, the finding of a higher exposure to alcohol and smoking in unaffected participants

compared to affected participants may be the result of successful intervention, as individuals who experienced childhood disease were advised to avoid alcohol and tobacco. Participants described worry and helplessness for both their own disease and their inability to ease the suffering of family members. Adverse consequences of HP on health-related quality of life, specifically daily activities/work and psychological well-being, were described by participants. HP had differing impact on family relationships and dynamics, which may reflect variable patterns of disease severity and outcomes in HP families.

Feelings of worry and helplessness were expressed by study participants. Many previous studies have found genetic diseases to be emotionally challenging for families (Dinc & Terzioglu, 2006; McAllister et al., 2007; Williams et al., 2009). Though a number of affected individuals expressed worry for their own health or finances, the majority of both affected and unaffected participants directed their worry toward other family members. This finding may be the result of a biased sample, where participants capable of completing the survey were less likely to have severe disease compared to other family members. Furthermore, the finding of lower depression scores in affected participants compared to unaffected family members was an interesting finding. However, further study is needed to replicate this finding in a larger cohort, to rule out potential study biases, and identify predictors of depression in individuals with HP and their family members. Still, these results suggest that distress and worry of parents and other family members should be monitored and appropriately addressed by genetic counselors and other providers. Sources of support and effective coping strategies should be provided to both affected individuals and their family members.

Responses suggest that the impact of HP on family relationships and dynamics may depend in part on the disease presentation in the family. Individuals with HP exhibit a striking variability in disease onset, severity, pain and risk for complications, which is further complicated by reduced penetrance. Parents may be burdened with worry and caretaker responsibilities for children. In contrast, children may grow up with a carrier parent or sibling who is severely disabled, has mild disease, or exhibits no symptoms. While there is a large body of research on the impact of caring for a child with disabilities on parents, children of parents with physical disabilities can also be adversely affected during key developmental periods and experience altered family roles and relationships (Iezzoni, Wint, Kuhlthau, & Boudreau, 2016; Williams et al., 2009). Studies on other conditions have shown that the effects of a family member’s disease on other family members often depends, in part, on their relationship to the affected individual (Lavelle, Wittenberg, Lamarand, & Prosser, 2014; Lieberman & Fisher, 1995; Wittenberg, Ritter, & Prosser, 2013; Wittenberg, Saada, & Prosser, 2013). In one study, the parents of affected children with various conditions were more likely to experience somatic health effects (e.g., physical pain, sleep disturbance) compared to both adolescent and adult children of an affected parent (Wittenberg, Saada, et al., 2013). Quantitative measures are needed to define the role of relationships in the impact of HP on family functioning.

Distress about the pain of family members and disabling pain appears to have effects on HP families, and pain management is critical to improve quality of life and functioning (Drewes et al., 2017; Machicado et al., 2017; Mullady et al., 2011; Olesen et al., 2014). However,

development of opioid dependence also has devastating consequences for patients and families. In contrast to other forms of chronic pancreatitis, HP is complicated by the need for pain management in adolescence, when there is a greater risk for dependence. However, addiction in HP is not well discussed in the literature. Despite alternative approaches to improve pain, including resection and nerve blocks, many patients require long term treatment with opioids (Nusrat, Yadav, & Bielefeldt, 2012). Furthermore, as with sickle cell disease, patients who present to emergency departments during pain attacks may be stigmatized as drug-seekers (Bulgin, Tanabe, & Jenerette, 2018; Goulden, 2013). This possibility is particularly concerning when traditional markers of a pancreatic attack (amylase and lipase) are no longer elevated due to extensive tissue damage, but patients still experience pain from fibrosis, enlarged and hypersensitive nerves and yet unknown mechanisms of pain generation. The long term effects of opioids have not been well studied, but recent studies suggest a potential for exacerbation of disease (Barlass et al., 2018) and development of opioid-induced hyperalgesia (Yi & Pryzbylkowski, 2015).

The majority of participants found ‘school or work limitations’ to be a moderately or extremely important financial concern. Chronic disease is a challenging barrier to educational attainment and maintaining a job, for which there are limited protections in the United States. For patients who are able to work, a career coach that specializes in chronic illness may provide guidance for informing and navigating adjustments with their employer or exploring alternative careers.

Agreement with reasons to pursue genetic testing were consistent with the previous study in this cohort from *Applebaum*, et al (2001), in which participants were asked to select the most important motivating factor to pursue genetic testing. In that study, ‘Seeing relatives affected with hereditary pancreatitis’ was ranked 1st (48%), followed by ‘To help my future generations’ (33%) (Applebaum-Shapiro, Peters, et al., 2001). As with the 2001 study, trends in ranking of reasons to pursue genetic testing were associated with helping others. In contrast, only 6.7% (1/15) indicated ‘the disturbing emotions prompted by witnessing a relative afflicted with HP’ v. 33% in the 2001 study. Except in cases of predictive testing or an undiagnosed family, this finding may reflect a lower impact of *PRSS1* genetic testing for affected individuals in established *PRSS1*-HP families. Further study is needed to understand how genetic testing impacts individuals with, at risk for, or suspected to have HP, particularly with the expansion of pancreatitis genetic risk panels. Interestingly, recall of transmission risks for *PRSS1*-HP was found to be lower than prior studies on recall of recurrence risks (72% recall after 8–10 years) (Somer, Mustonen, & Norio, 1988). However, a distinction between perceived risk to pass on the gene mutation (50%) versus the risk to have a child that both inherits the *PRSS1* pathogenic variant and develops pancreatitis (40%) could not be determined from the study question.

With regard to genetic counseling, participants generally wanted to receive information that is typical of a genetic counseling session, including information that has already been recommended in consensus guidelines (e.g. pancreatic cancer screening) (Ellis, 2004; Ellis et al., 2001). Participant responses describing the ‘content’ of the genetic counseling session as the most useful aspect are consistent with the findings of Bartels, *et al.*, who found that

77% of participants reported ‘content’ as the most helpful aspect of genetic counseling (Veach, Truesdell, LeRoy, & Bartels, 1999).

Practice Implications

A long-term relationship with a multidisciplinary team in a specialty clinic, such as a National Pancreas Foundation Pancreatitis Center of Excellence, is necessary to address the implications of disease at different life stages – e.g. childhood onset of pancreatic attacks, family planning, and risk for pancreatic cancer in adulthood. All clinicians should be aware of and monitor risk for opioid dependence, as well as be observant of unhealthy coping strategies that must be addressed. A discussion of effective coping strategies is indicated for both affected individuals and their close family members, particularly to address distress, worry, and reduced quality of life. The finding of financial concerns, particularly ‘school or work limitations’, indicates that access to a social worker, financial advisor and/or career coach may benefit some patients.

Genetic counselors and clinicians must be sensitive to the expression and pattern of disease within each family. In addition to the implications of family history on risk and outcomes, perceptions of risk and fear of potential outcomes may be directly related to the penetrance and severity of disease in the family. Familial psychosocial counseling should be significantly influenced by the family structure of unaffected and affected individuals. As seen in the qualitative data, the familial implications of an unaffected parent and severely affected child are distinct from the relationship between a severely affected parent and a healthy child.

Limited clinician education on and recognition of HP has a negative impact on these patients who require immediate intravenous fluids and pain management during pancreatic attacks. Historically, pancreatitis in adults was believed to always be caused by alcohol abuse. Despite the recognition of HP as a genetic disease, the response of the participant classified in the ‘Other’ category under ‘Most Difficult Problems Due to HP’ suggests that perceptions of pancreatitis patients as alcoholics may still persist. Families with HP in the United States are most commonly European and descended from a founder population in Appalachia, where the majority of families with HP remain (Applebaum-Shapiro, Finch, et al., 2001). Many of these individuals are receiving emergent care for pain attacks at rural centers, which may be unfamiliar with HP. Further awareness of proper management of HP pain, clinical presentation of patients with later stage disease, de-stigmatization of these patients as alcoholics or drug-seekers, and improved guidelines for treatment of HP patients who present to emergency departments for severe pain is needed.

Study Limitations and Research Recommendations

HP is a rare genetic disease with reduced penetrance. As with other rare diseases, sample size is limited by the prevalence of disease and the ability to diagnose and recruit such individuals into a research study. This challenge was further compounded in this historical study by loss to follow-up due to outdated contact information. The small sample size of this study limits the generalizability of these findings. Furthermore, this sample may be biased toward individuals with less severe disease who are able to complete the survey.

Confirmation of these findings is needed in a larger sample size, which would also allow for subgroup comparisons. Additional data on time elapsed from genetic counseling will be important for assessing recall and education strategies in this population. Although affected participants reported on pain level and pattern, quantitative measurements of disease severity were not collected in affected, non-participant family members described by unaffected participants in this study. Therefore, quantitative measurements of disease severity could not be correlated with participant responses.

The qualitative data in this study is limited by lack of depth. Answers to short answer questions provided some initial themes that are relevant to families with HP. A further exploration of these themes, as well as other issues that are important for HP families, is needed through in-depth interviews. The current study provides preliminary data to guide future study designs, as well as initial themes that researchers should be sensitive to when conducting interviews.

Future studies to collect data on perspectives and current practices of both genetic counselors and physicians are indicated to examine the variability of care and provide insight for improved patient management guidelines.

Conclusion

Recommendations for genetic counseling for HP have been published in two prior studies (Ellis, 2004; Ellis et al., 2001). However, only one prior study evaluated motivations of this patient population to participate in research and pursue genetic testing (Applebaum-Shapiro, Peters, et al., 2001). In the current study, the finding that the majority of affected adults with HP and their unaffected family members are concerned about school and work limitations suggests that HP families may benefit from access to a social worker, financial advisor and/or career coach. Deficits in recall of transmission risks for *PRSS1*-HP indicate the need for improved patient education strategies, such as re-education at multiple stages of life. Counseling strategies and goals must adapt to the varied disease presentation in HP families, particularly to address these nuanced effects on individuals and family dynamics. The expression of worry for other family members from both affected and unaffected participants indicates the need for psychosocial support for individuals with HP and their family members. Moreover, the reporting of opioid dependence and additional drug abuse by multiple participants is an important finding, for which patients should be monitored. A summary of identified counseling issues for HP that should be considered are provided in Table 5.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant Characteristics

Variable	Affected Participants (n=39)	Unaffected Participants (n=21)	P-value
Male sex, N (%)	17 (43.6%)	7 (33.3%)	0.62
Age, mean (SD; median) **Range**	53.7 (20; 56.8) Range 21.7–91.5	58.2 (16.4; 60.1) Range 22.7–88.3	0.42
BMI, mean (SD; median)	25.9 (5.1;24.4)	26.0 (6.8; 24.8)	0.76
≤ 25 kg/m^2	25 (64.1%)	11 (52.4%)	0.70
26 – 29 kg/m^2	6 (15.4%)	6 (28.6%)	
≥ 30 kg/m^2	8 (20.5%)	4 (19.0%)	
Smoking Status			0.13
Never	26 (66.7%)	9 (42.9%)	
Ever	13 (33.3%)	12 (57.1%)	
Ever Drinker			0.06
No	13 (33.3%)	2 (9.5%)	
Yes	26 (66.7%)	19 (90.5%)	
Familial *PRSS1* Mutation *			0.23
PRSS1 p.R122H	30 (76.9%)	20 (95.2%)	
PRSS1 p.N29I	5 (12.8%)	1 (4.8%)	
Only Clinical Criteria Met	4 (76.9%)	0	
Chronic Pancreatitis	20 (51.3%)	0	NA

* 7 unaffected participants were identified as asymptomatic *PRSS1* carriers

Table 2.

Level of Importance for Financial Concerns

Concern	Participants	n	Not at all important	Slightly/Somewhat important	Moderately/Extremely important
School or work limitations	Affected	36	11 (31%)	3 (8%)	22 (61%)
	Unaffected	19	3 (16%)	2 (11%)	14 (74%)
Cost of medical treatment	Affected	37	6 (16%)	14 (38%)	17 (46%)
	Unaffected	19	1 (5%)	7 (37%)	11 (58%)
Costs of surgery	Affected	37	8 (22%)	13 (35%)	16 (43%)
	Unaffected	19	1 (5%)	7 (37%)	11 (58%)
Requiring caretakers	Affected	37	13 (35%)	15 (41%)	9 (24%)
	Unaffected	19	5 (26%)	5 (26%)	9 (47%)

Table 3.

Level of Agreement for Reasons to Pursue Genetic Testing

Concern	Participants	n	Strongly/somewhat disagree	Neutral	Strongly/somewhat agree
To help others through research	Affected	37	1 (3%)	0	36 (97%)
	Unaffected	21	0	0	21 (100%)
To help one's future generations	Affected	37	0	2 (5%)	35 (95%)
	Unaffected	21	0	0	21 (100%)
Improvement of personal medical care	Affected	37	0	2 (5%)	35 (95%)
	Unaffected	21	0	3 (14%)	18 (86%)
To learn more about yourself	Affected	37	0	2 (5%)	35 (95%)
	Unaffected	21	0	3 (14%)	18 (86%)
Presymptomatic testing to reduce uncertainty or anxiety	Affected	37	0	6 (16%)	31 (84%)
	Unaffected	20	0	2 (10%)	18 (90%)
The disturbing emotions prompted by witnessing a relative afflicted with HP	Affected	37	0	11 (31%)	25 (69%)
	Unaffected	20	1 (5%)	1 (5%)	18 (90%)
Pressure from relatives	Affected	37	5 (14%)	23 (66%)	7 (20%)
	Unaffected	21	6 (33%)	8 (44%)	4 (22%)

Table 4.

Major Topics Participants Believed Should be Provided by a Genetic Counselor Regarding Hereditary Pancreatitis

Major Topic	Representative Quote(s)
Inheritance	"Likelihood of passing HP to my offspring." Participant 005, affected "How is this passed down to family members…?" Participant 043, unaffected
Disease natural history and outcomes	"The care and maybe what to expect." Participant 004, affected
Treatment and management strategies	"Description of disease. Options for treatment. How to further gain help for pancreatitis." Participant 016, affected Treatment options, how to avoid/minimize attacks, long-term health prognosis." Participant 050, affected "The important of – and best methods for – annual testing for early indications of pancreatic cancer." Participant 049, affected
Resources	"…possible support materials or support groups." Participant 058, unaffected.
Information regarding genetic testing	"What to do with the info after you get your results." Participant 040, affected
New research findings	"All scientific studies and discoveries for the treatment and cure of this extremely painful and life altering disease." Participant 18, affected
Family planning	"Is there a way to have a child and remove the chance of passing down hereditary pancreatitis? Besides luck?" Participant 041, affected
Lifestyle modifications	"Nutrition counseling. What foods can be digested easier and how should they be prepared. Should everything go in a blender?" Participant 024, affected "Don't overlook the importance that STRESS plays in the activation of an attack to someone who has HP…" Participant 041, affected
Mental Health Implications	"That depression usually comes with it and family members should know the signs of depression." Participant 022, unaffected

Table 5.

Counseling Issues to Consider for Hereditary Pancreatitis

Pain	Importance of pain management for daily living Risk and impact of opioid dependence
Quality of Life	Activities of living Psychosocial well-being; mental health
Family Dynamics	Impact of loss Altered family roles according to affected status and severity in family
Worry	Feelings of helplessness and worry for both patients and family members Importance of support and healthy coping strategies
Pancreatic Cancer	Risk, including from family history and lifestyle risk factors
Stigmatization	Adverse experiences of individuals with HP with healthcare professionals e.g. stigmatization as drug-seekers or alcoholics
Financial Concerns	Concerns regarding school and work limitations