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Hereditary pancreatitis – Assesment and Clinical Management

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ABSTRACT: Hereditary pancreatitis (HP) is an autosomal dominant disorder characterised by recurring acute pancreatitis events that progress to chronic pancreatitis over a variable time period. It causes repeated acute pancreatitis events, which commonly lead to chronic pancreatitis at a young age. The cationic trypsinogen gene has two mutations (R122H and N29I), which are seen in the majority of people with hereditary pancreatitis (PRSS1 gene). One of these changes, the R122H mutation, is thought to induce pancreatitis by changing a trypsin recognition site, blocking trypsin deactivation and extending its action, resulting in auto digestion. There are families with these two mutations in various countries, and there are also additional uncommon mutations connected to hereditary pancreatitis. Hereditary pancreatitis manifests itself in the same way as sporadic pancreatitis, but at a younger age. It is typical for people to go years without being identified, especially if they have non-specific symptoms. Patients with recurrent pancreatitis and a family history of pancreatic illness should always be examined for hereditary pancreatitis. When comparing patients with the two prevalent variants, those with the R122H mutation are more likely to appear at a younger age and require surgical intervention than those with the N29I mutation. Hereditary pancreatitis is associated with a 40% lifetime risk of pancreatic cancer, with people aged 50 to 70 being the most vulnerable and for whom screening testing may be necessary.

I. INTRODUCTION

Hereditary pancreatitis (HP) is a rare cause of acute, recurrent acute, and chronic pancreatitis, which is similar to other causes of pancreatitis, including alcohol, gallstones, autoimmune conditions, anatomical variations such pancreas divisum, or hypertriglyceridemia. Exocrine and/or endocrine insufficiency may develop over time, with symptoms often beginning in infancy or adolescence. Hereditary pancreatitis' clinical spectrum was initially described in 1952 [1]. HP-causing mutations have been discovered in the PRSS1 gene, which codes for cationic trypsinogen [16,3,4] .The genetics of HP, as well as its pathophysiology and clinical range, are discussed in this article.

❖ History

The lineage of a family with four people who had been diagnosed with chronic relapsing pancreatitis and two further members who had the disease's likely cause was described in 1952. [2] These six individuals of the same family, who span three generations, all had pancreatitis at or before the third decade of life and had comparable symptoms and aftereffects in an autosomal dominant pattern. This was the earliest account of HP in any literary work. In 1971, HP was defined as - inflammation of the pancreas, usually recurrent from childhood, with unusual prevalence among blood-related groups of persons in accordance with Mendelian laws. [3] 100 other families with several generations of people with HP were mentioned in the literature over the course of the following several decades. [4–10] A big family with 47 HP patients underwent a genome segregation analysis in 1996, which resulted in the identification of multiple chromosomal markers on the long arm of chromosome 7 [11]. This was the first step toward the identification of an HP gene. Following the confirmation of this research by two other groups [12,13], the first genetic error linked to HP was discovered. This flaw was caused by the R122H mutation of PRSS1, which is an arginine to histidine substitution in codon 122 of the cationic trypsinogen serine protease 1 gene. [14]

❖ Epidemiology

A significant morbidity and financial burden are associated with chronic pancreatitis. Chronic pancreatitis is ranked as the sixth most

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prevalent digestive condition among hospitalised patients, with expenses associated with care exceeding $3 billion, according to studies from the National Institutes of Health database. [15] In the US, chronic pancreatitis is estimated to affect 5–14/100,000 persons annually, with a prevalence of 50/100,000 people. [16] Alcohol usage was recently found to be the most frequent etiological factor in chronic pancreatitis, accounting for 44.5 % of cases; genetic variables accounted for 8.7 % of cases under the category of "non-alcohol" etiologies. [17] According to estimates, the prevalence of HP is 0.57/100,000 in Denmark, 0.125/100,000 in Germany, and 0.3/100,000 in France. [18,19] This literature does not provide any estimates of the prevalence on a global scale. However, because to the rarity of testing outside of specialised facilities, these figures probably underestimate the real frequency of HP. Children who had previously been diagnosed with idiopathic acute, recurrent acute and chronic pancreatitis in 2015 were 33 %, 45.4 %, and 54.4 % more likely to have a genetic cause. [20] One of the key factors causing pancreatitis in children is HP. The average age of diagnosis for chronic pancreatitis is caused by causes other than alcohol was 64 years old, according to a population-based study. [21] According to research, chronic pancreatitis often develops throughout the first two decades of life, with the median age at diagnosis of HP falling between 5 and 19 years. [19,22]

❖ PATHOPHYSIOLOGY

For numerous reasons, the mechanism by which mutations in the cationic trypsinogen gene induce hereditary pancreatitis is crucial. Firstly, the cellular processes underlying acute pancreatitis and the transition to chronic pancreatitis remain unknown. Secondly, it is unknown why one person's pancreas is vulnerable to alcohol while another's pancreas is not. Thirdly, concentrating on the genetic relationship between pancreatitis and pancreatic cancer, which can develop as a complication in both sporadic and hereditary pancreatitis, may give insight into the genesis of pancreatic cancer. The pancreatic acinar cell secretes trypsinogen [15]. Enterokinase converts it to trypsin in the duodenum, cleaving an 8-aminoacid N-terminal peptide. A cascade of digestive enzyme precursors is subsequently activated by trypsin. There are many systems in place to prevent trypsin from being activated inappropriately in the pancreas before it is secreted into the duodenum. The R122H mutation is thought to modify a trypsin recognition site, preventing trypsin deactivation within the pancreas and so extending its action [16]. The mechanism causing pancreatitis by the N29I mutation is unknown. However, it has been hypothesised that the N29I mutation might promote trypsinogen autoactivation by affecting the binding of pancreatic secretory trypsin inhibitor (PSTI) [3] or impairing trypsin inactivation by altering the accessibility of the first hydrolysis site to trypsin. This is supported by predicted molecular conformational changes in the structure of trypsin [16]. The pathogenic mechanism by which the A16V mutation induces pancreatitis is unknown; however it is thought to affect the signal peptide's cleavage site [12]. Because the two most prevalent mutations, R122H and N29I, give such a similar clinical picture, it's been suggested that rather than being the cause of hereditary pancreatitis, these mutations are just markers for a variety of related pancreatic abnormalities. However, there is little question that in the vast majority of instances, improper prevention of trypsin deactivation inside the pancreas is the cause of HP. Few studies show that cationic trypsinogen gene mutations have a penetrance of around 80%. A study of monozygotic twins with HP was conducted to identify variables leading to this [17]. Seven sets of twins were qualified for this investigation out of a total of eleven sets. Four of the seven sets of twins were concordant for pancreatitis, whereas three of the seven sets of twins (43 %) were discordant for pancreatitis phenotypic expression. In the seven pairs of twins, the total penetrance was 78 %. The researchers concluded that genetic and/or environmental variables play a role in HP expression and onset age. The mechanism of non-penetrance is yet unknown.

❖ THE GENETICS OF HEREDITARY PANCREATITIS

HP is an autosomal dominant disease with an 80% penetrance rate. When it was proven in 1996 that the hereditary pancreatitis gene could be traced to chromosome 7q35, [5, 6] the exact mutations responsible for HP were found. Whitcomb et al discovered a mutation in the third exon of the cationic trypsinogen gene (PRSS1) in these individuals [7]. The mutation, a guanine (G) to adenine (A) transition, changes arganine (CGC) to histidine (CAC) at codon 117 (using the chymotrypsin numbering scheme) is also known as R117H mutation. Because it provides a new recognition site for the restriction endonuclease

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AflIII, the initial mutation is quickly discovered. A neutral variation inside this enzyme recognition site has recently been found to cause a false negative result [8]. Single adenine (A) to thiamine (T) transversion mutation in exon 2 resulted in an asparagine (ACC) to isoleucine (ATC) substitution at amino acid 21[3]. A second mutation in the cationic trypsinogen gene was reported later. These two variants (R117H and N21I) have now been found in hereditary pancreatitis families from various countries, including France[4], Germany[9], the United Kingdom [10], Japan[11], and the United States [3,7]. The A16V variant, which was first discovered in three individuals with idiopathic pancreatitis and one patient with HP [12], appears to be a considerably less prevalent mutation. There is additional evidence that HP is linked to mutations in genes other than the cationic trypsinogen gene [13]. A new naming scheme for human gene mutations has been created and approved since the discovery of the cationic trypsinogen gene alterations. The nomenclature of the frequent mutations have been altered from R117H to R122H and N21I to N29I.

❖ **Genetic features**

The symptoms of HP are believed to be caused by genetic abnormalities that lead to an imbalance of naturally released proteases and their inhibitors, which culminates in autodigestion of the pancreatic parenchyma. Numerous genetic abnormalities have been found and the HP inheritance patterns have been documented since the first mutation was revealed in 1996. [14] The penetrance of these mutations might vary, although it is usually rather high. The autosomal dominant pattern, which results from the acquisition of a single defective parental gene, is the most frequent form of HP inheritance. The mutations in the PRSS1 gene are most frequently linked to this pattern. Rarely do other mutations that cause HP have an autosomal dominant inheritance pattern. A pedigree examination of a Polish family with 14 individuals over four generations who had been diagnosed with HP in 2009 revealed that this family has a novel, undiscovered mutation with an 80% penetrance; genetic locus analysis is being conducted for this mutation. [24] A novel one-base deletion in exon 1 of the serine protease inhibitor Kazal type 1 gene (SPINK1 c.27delC), which is also passed on in an autosomal dominant manner, was discovered in HP patients using a whole exome sequencing approach. [25] A less frequent inheritance form for HP is autosomal recessive HP, which requires two defective parental genes for the onset of symptoms. This is how HP is inherited, including some of the mutations in SPINK1 and the cystic fibrosis gene. The last form of inheritance pattern that has been documented in the literature is a complicated one in which a patient must also have a genetic defect, or a combination of genetic abnormalities, in order to manifest clinically as HP. For instance, in 2010 it was shown that the co-occurrence of the genetic variations SPINK1 and an uncommon variant of the cystic fibrosis gene (CFTR p.R75Q) enhanced the risk of HP. However, a normal phenotype without signs of pancreatitis was the outcome if the cystic fibrosis variation was inherited alone. [26]

- **PRSS1**

It has been discovered that the PRSS1 gene is mutated in up to 80% of HP patients. [19, 23,27–29] The most prevalent isoform of trypsin released by the pancreas, cationic trypsin, is encoded by PRSS1. When triggered by food intake, cationic trypsin transforms dormant pancreatic zymogens released by the pancreas into active digestive enzymes in the duodenum. The inactive form of trypsin is called trypsinogen. The digestive enzymes are prematurely activated when trypsinogen is converted to trypsin before they are excreted from the pancreas. This autodigestion of the parenchyma causes inflammation and injury, which are clinically recognised as pancreatitis. The early conversion of trypsinogen to trypsin is prevented by a number of physiological defence mechanisms. Clinical pancreatitis may result from genetic changes in the PRSS1 gene that disrupt these defensive systems. There are already more than 20 PRSS1 mutations linked to HP that have been reported [14,30-38]. The majority of these mutations are found in the PRSS1 gene's sections that encode trypsin's two primary regulatory domains, one of which governs the conversion of trypsinogen into trypsin and the other of which governs the elimination of active trypsin. The R122H mutation (78 percent of mutations, with a penetrance of 80 percent), the N29I mutation (12 percent of mutations, with a penetrance of 93 percent), [19,39] and the A16V mutation are the three most prevalent variants on PRSS1 (the third most common mutation, with a penetrance of 43 percent). [35] The R122H mutation is a gain-of-function mutation that affects the destruction regulation site; it inhibits trypsin from undergoing autolysis, increasing its stability and raising its levels in the pancreas, which promotes the

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activation of additional digestive enzymes and pancreatic autodigestion. [34] The N29I mutation affects the other regulatory site, resulting in higher and improper trypsin autoactivation, elevated trypsin levels, and enhanced pancreatic autodigestion. [33] Thus, HP brought on by either R122H or N29I PRSS1 mutations may manifest clinically in a comparable manner. 27 individuals with HP caused by the R122H or N291 mutations showed no variations in their clinical presentation. The majority of individuals who had these mutations also had minimal illness. [40] The A16V mutation's mode of action is not as well understood. The trypsinogen protein is released in its usual amount and shape despite the fact that this mutation results in an aberrant amino acid being present in the cleavage site of the mature trypsinogen protein [31]. [32] There is proof that the A16V mutation causes a fourfold increase in trypsin activation by increasing the secretion of the chymotrypsin C (CTRC) protein. [41] This shows that, in contrast to the autosomal dominant R122H and N291 mutations, the A16V mutation is inherited in a complicated fashion and may need the coinheritance of additional mutations to result in clinical pancreatitis.

- **SPINK1**

SPINK1 has also been identified as an HP-causing gene. This gene produces an acute-phase protein, a trypsin inhibitor, which is produced in pancreatic acinar cells and has the function of preventing autodigestion of the pancreatic parenchyma and inhibiting the activation of digestive enzymes by prematurely converted trypsin. Loss-of-function mutations in SPINK1 therefore result in lower amounts of the inhibitor protein and raise the risk of developing pancreatitis. [27,42] The N34S mutation, P55S mutation (more prevalent in Europe and the US), and IVS3 + 2TC mutation (more common in Asia) are the most common SPINK1 mutations linked with HP . [43] Although these SPINK1 mutations may, in a few number of cases, directly contribute to the emergence of HP, [44] their presence may raise the risk of pancreatitis by up to 23%. [45–47] Although at least one SPINK1 mutation (SPINK1 c.27delC) may be inherited in an autosomal dominant pattern, it is believed that few SPINK1 mutations that are directly linked to the development of HP are inherited in an autosomal recessive manner [25,46] The phenotypic expression of pancreatitis may need interactions with other inherited genetic mutations and/or environmental conditions in order to produce HP when they are inherited in a heterozygous form, as is the case the majority of the time. [44, 46, 48–50] SPINK1 mutations are therefore frequently regarded as disease-modifying mutations.

- **CFTR**

HP is also linked to mutations in the CFTR gene, which regulates transmembrane conductance in cystic fibrosis. The respiratory system, sweat glands, gallbladder, and pancreas all need the CFTR protein to transport salt, chloride, and bicarbonate across epithelial surfaces. The multisystem illness known as cystic fibrosis is brought on by CFTR mutations and is characterised by thicker and profuse secretions that impair mucociliary clearance and lead to lung damage and infection. Due to reduced pancreatic fluid volumes, it can also result in decreased insulin and digesting enzyme release. Additionally, the pancreatic lumen's elevated acidity might precipitate proteins that block the pancreatic ducts. Diabetes mellitus, which is present in >50% of cystic fibrosis patients over the age of 30 years, as well as pancreatic exocrine insufficiency, which is present in 85%-95% of cystic fibrosis patients, are the outcomes of this confluence of pancreatic disorders. [51] It has been calculated that 10% to 20% of the remaining cystic fibrosis patients may develop pancreatitis if their pancreatic parenchyma is sufficiently preserved. Therefore, pancreatitis may occur in 1.5% of cystic fibrosis patients at some time in their life. [52,53] Aside from the cystic fibrosis disease, CFTR mutations can also result in pancreatitis. [52,54] There are more than 2,000 known CFTR mutations. An autosomal recessive inheritance of severe homozygous mutations, such as F508-delta/F508-delta, leads to the classic multisystem cystic fibrosis phenotype, which frequently includes early-onset pancreatic insufficiency. Recurrent acute pancreatitis in the form of HP occurs seldom in patients with this kind of heredity. [55] In contrast, inheriting a moderate variety of CFTR, such as the R75Q mutation, is linked to a more constrained form of the disease and a higher prevalence of pancreatitis. In 2005, it was shown that individuals with the R75Q mutation had a 40–80-fold higher chance of getting pancreatitis than people without the mutation. [56] Additionally, nine CFTR variants (known as CFTR-BD mutations) that are linked to a deficit in bicarbonate conductance and carry a risk of acute and chronic pancreatitis in the context of a

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moderate cystic fibrosis condition were found. [57] Finally, some CFTR mutations can be passed down through families in a complicated manner. A patient is more likely to develop pancreatitis if they are heterozygous for, say, one CFTR mutation and another genetic mutation like SPINK1 or CTRC. [26,58]

- **CTRC**

It has been discovered that the protease CTRC, which is released by pancreatic acinar cells, also breaks down trypsin and trypsinogen. [41] The stimulation of digestive enzymes by trypsin and pancreatic autodigestion that results in pancreatitis are examples of alternative defensive mechanisms. Reduced CTRC secretion, increased trypsin degradation, a catalytic deficiency in the CTRC protein, and other processes all contribute to the loss of function brought on by CTRC mutations. [59–61] Four pathogenic variations, including A73T, V235I, R253W, and K247 R254del, as well as several CTRC mutations that operate through the above mentioned methods which have been characterised. Ten more possible pathogenic CTRC variants were found. [60] Similar to SPINK1 mutations, CTRC mutations may not directly cause HP, but they may raise the risk due to interactions with SPINK1 or CFTR mutations, as well as environmental variables and other mutations. [60] Numerous research have looked at the incidence and magnitude of CTRC mutations in chronic pancreatitis patients in Europe, India, and Asia. Although these mutations don't seem to be particularly frequent in HP patients (1 percent to 3 percent), they do appear to have a considerable impact size, increasing the probability of acquiring HP by four to eight times. [58–63]

- **Others genetic mutations and copy number variants**

HP is thought to be caused by a number of less well-studied genes that become mutated. [64] One of these genes, cathepsin B (CTSB), is hypothesised to cause trypsinogen to be activated too early in the course of a mutation. One research published in 2006 [65] hypothesised that pancreatitis was caused by SPINK1 and CTSB mutations, however a subsequent investigation was unable to support this hypothesis. [66] The calcium-sensing receptor gene, or CASR, is essential for preserving calcium homeostasis as well as the stability of trypsinogen and trypsin. Numerous studies suggest that a patient is predisposed to pancreatitis via a complicated inheritance pattern when this gene is mutated. [67,68] In addition, a genome-wide susceptibility research discovered that a high-risk mutation in the claudin-2 (CLDN-2) gene on the X chromosome is strongly linked to an elevated risk for recurrent acute pancreatitis. [69] Mutations in CLDN-2 seem to be inherited in an autosomal dominant manner in males and in an autosomal recessive pattern in women because of its placement on the X-chromosome. [69–71] In the carboxypeptidase A1 (CPA1), a second high-risk genetic flaw has been identified that may enhance the chance of developing pancreatitis owing to a misfolding of the trypsin protein. [72] Finally, recent research have looked at the link between known gene copy number variants and the emergence of HP. In individuals with HP, it was discovered that many exons on the PRSS1 gene and two exons on PRSS2 (which codes for anionic trypsinogen, a protein with properties similar to cationic trypsinogen) were duplicated, resulting in gain-of-function mutations that boost the production of trypsinogen. [73] Additionally, two SPINK1 copy number gene alterations linked to a trypsin inhibitor's lack of function were reported. [74] The Chronic Pancreatitis Genetics Risk Factors Database is updated with these additional variations when further genetic mutations connected to HP are found. In the most prevalent genes linked to HP, it provides an updated and thorough list of all known genetic mutations, both pathogenic and nonpathologic. [75]

❖ **Clinical features**

HP can begin as recurrent acute pancreatitis with pancreatic inflammation, which is characterised by the abrupt onset of nausea, vomiting, and abdominal discomfort. The discomfort may radiate to the back and be postprandial, coming from the epigastric area. There are no published statistics on the frequency of pancreatitis attacks in HP. The pancreas is thought to experience increased duct distortion and parenchymal damage over time as the frequency of recurrences rises. Fibrosis, parenchymal calcification, ductal stricture, and peripancreatic fluid collections are examples of chronic pancreatitis manifestations that might appear. Due to pancreatic exocrine insufficiency, malabsorption, and steatorrhea, as well as pancreatic endocrine insufficiency and diabetes mellitus, these morphologic changes can result in clinical complications. These clinical complications include biliary obstruction, pancreatic duct stone formation,

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malabsorption, and steatorrhea. It is typical for these consequences to cause weight loss, persistent discomfort, recurrent hospitalizations, and other interactions with the medical system. [23] The clinical characteristics of HP that could manifest over the course of the disease's natural history have been explored to describe in two significant investigations. 200 French individuals with HP were assessed in 2009, while 418 patients with HP from various nations were defined in 2004. 83 percent of the patients had epigastric discomfort, whereas 23 percent had pseudocysts, 61 percent had calcifications, 35 percent to 37 percent had pancreatic exocrine insufficiency, and 26 percent to 32 percent had diabetes mellitus. [1,19] 60 percent of individuals with diabetes mellitus had an insulin dependency. [19] Although these HP symptoms resemble those brought on by other acute and chronic pancreatitis, there are several key differences. HP typically manifests early in life, frequently in the first two decades of life, as was previously mentioned. Patients with the R122H mutation of the PRSS1 gene as opposed to patients with HP caused by other genetic mutations likely to have a younger age of illness onset than those with a paternal inheritance pattern (9 years of age versus 14 years of age) [1,19]. The disease's early start may provide particular difficulties for the sufferers and their families. Compared to adult-onset disease, the long-term course of childhood-onset disease may also come with additional financial and psychological difficulties. The cumulative risk of exocrine insufficiency and diabetes is greater in HP than in other types of pancreatitis, despite the fact that the time to develop exocrine and endocrine failure did not differ between patients with HP and those with "mutation-negative" pancreatitis (60.2 percent and 68.6 percent , respectively). [1] In comparison to the general population, those with HP also have a much higher chance of acquiring pancreatic cancer. While the French cohort estimated the SIR of pancreatic cancer in HP to be 87, the EUROPAC study discovered a SIR of 67 [1,19]

❖ CLINICAL PRESENTATION IN HEREDITARY PANCREATITIS

A patient with HP frequently presents with symptoms that are similar to the case of sporadic pancreatitis. The clinical presentation varies, but typical individuals have repeated acute pancreatitis episodes in childhood, which develop to chronic pancreatitis later [1,18]. During an acute episode, the symptoms are identical to those of gallstone-induced, alcoholic, or idiopathic acute pancreatitis. In these individuals, chronic pancreatitis seems to be indistinguishable from alcoholic, idiopathic, or other types of chronic pancreatitis [18-20]. The appearance of HP in pediatric patients is similar to that of idiopathic juvenile chronic pancreatitis [21]. However, it is quite typical for these people to be untreated for many years, despite the fact that they have often had chronic symptoms from childhood. We've discovered that when the condition is recognised within a family, numerous members are diagnosed with pancreatitis for the first time, after previously being labelled with "peptic ulcer" or "chronic abdominal pain." The pancreatic clinic in Newcastle upon Tyne, UK, now contains patients with hereditary pancreatitis from thirteen different families. Nine of these families have previously been studied [10]. The R122H (R117H) mutation was discovered in three families, while the N29I (N21I) mutation was found in five more. In the remaining family, no mutations were found in any of the PRSS1 gene's five exons. The R122H group's families and patients were compared to the N29I group's families and patients. A comparison of clinical information, including pancreatitis consequences, was performed. The R122H group had a shorter mean age at commencement of pancreatitis symptoms, 8.4 versus 6.5 years ($P = 0.007$), and more individuals with the R122H mutation experienced symptoms by the age of 20 years (89 vs 64 %). Surgical intervention was necessary in more individuals with the R122H mutation (8 of 12 vs 4 of 17, $P = 0.029$) and at a younger age. Exocrine failure was also more common in individuals with the R122H mutation, although the frequency and age of endocrine failure (as judged by the development of insulin-dependent diabetes mellitus) were equal in both groups. Both groups of patients reported alcohol as a triggering factor for their symptoms. These findings were also mentioned in the initial N21I mutation description in 1997 [3], as well as by the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) [22]. It is also known that, in addition to the mechanism of clinical manifestation, hereditary pancreatitis shares the same radiological and histological characteristics as other types of pancreatitis [23]. Aside from the early start and delayed diagnosis, hereditary pancreatitis has been reported to have a natural history that is comparable to chronic alcoholic pancreatitis in terms of pancreatic calcification, endocrine and exocrine pancreatic

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insufficiency, but a greater prevalence of pseudocysts [24].

❖ CATIONIC TRYPSINOGEN GENE MUTATIONS IN NON-HEREDITARY PANCREATITIS

Because the majority of individuals with cationic trypsinogen gene mutations have a documented family history of pancreatitis, taking a family history is particularly crucial in all patients with pancreatitis. Patients with so-called idiopathic pancreatitis, on the other hand, are frequently sent to a pancreatic specialist without a reliable family history [24]. It's also been speculated that PRSS1 gene mutations might cause idiopathic chronic pancreatitis. A study of 21 individuals with chronic alcoholic pancreatitis found no indication of the R122H or N29I mutation, but a far bigger and more relevant research looked at 221 patients with idiopathic chronic pancreatitis who had no family history of the disease. [25] In these cases, the full PRSS1 gene was sequenced. Only three individuals tested positive for mutations, one with R122H and two with A16V [26]. In individuals with idiopathic juvenile chronic pancreatitis, a condition that closely resembles the clinical pattern of hereditary pancreatitis, a genetic foundation has also been investigated [27]. One patient with idiopathic juvenile chronic pancreatitis had the R122H mutation, and another patient had the A16V mutation. These findings show that novel mutations do arise, and that screening for cationic trypsinogen gene alterations in people with idiopathic pancreatitis is worthwhile. Following the removal of alternative reasons, we do genetic counselling and genetic testing in patients with idiopathic pancreatitis. Patients have expressed an interest in learning about their genetic status in regards to this condition.

❖ RISK OF CANCER IN HEREDITARY PANCREATITIS

Pancreatic cancer risk is greatly elevated in people who have sporadic chronic pancreatitis. A multi-centre historical cohort analysis of over 2000 patients [28] strongly proved this. The standardised incidence ratio, or the ratio of pancreatic tumours seen to predicted, was 16.5. Increased surveillance of chronic pancreatitis patients may have increased the number of malignancies identified relative to the general population, resulting in detection bias in this study. However, a study of Swedish patients found that sporadic chronic pancreatitis is associated with an elevated risk of pancreatic cancer, with a standardised incidence ratio of 3.8 [29]. Patients with HP were not included in any of these trials, although the International Hereditary Pancreatitis Study Group has subsequently looked into their risk of getting pancreatic cancer. A total of 246 individuals with hereditary pancreatitis from eleven countries were identified, with an average follow-up length of more than 14 years [30]. There were eight individuals with pancreatic adenocarcinoma, with a standardised incidence ratio of 53.3. In these patients, the estimated cumulative risk of pancreatic cancer developing was about 40%, and the risk was higher in those with a paternal inheritance pattern. The Midwest Multicentre Pancreatic Study Group [31] has corroborated these findings. According to the findings of these cancer studies, chronic pancreatitis is a risk factor for pancreatic cancer, and hereditary pancreatitis puts individuals at an even higher risk of getting cancer than spontaneous pancreatitis. Although it is unclear if the increased risk of cancer is attributable to persistent inflammatory changes or the existence of a cationic trypsinogen mutation per se, the evidence now available shows that people with HP who acquire cancer have a long history of chronic pancreatitis [31]. Because of the large number of malignancies that have emerged in HP patients, it has been unable to determine which mutation(s) may predispose to cancer more than others. This information, on the other hand, will become available over time. The R122H mutation has not been linked to pancreatic cancer in 34 individuals with sporadic ductal adenocarcinoma, according to a study of pancreatic tissue from 34 patients with sporadic ductal adenocarcinoma [32]. As tissue from individuals with hereditary pancreatitis becomes accessible for study, more of these investigations are expected.

- **Pancreatic cancer**

HP of any origin provides a markedly elevated risk of pancreatic cancer regardless of the genetic mutation. However, HP is only partially responsible for pancreatic cancer cases overall. The actual and anticipated rates of pancreatic cancer in 246 individuals with HP from various nations were examined in 1997. In HP patients, the SIR for pancreatic cancer was 53. Prior to the age of 50, there was a relatively low cumulative risk of pancreatic cancer, which increased to 40% by the age of 70. A few decades after the initial presentation, the risk rises and seems to affect men and women equally. [76] These results were

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supported by later research; however, in other study groups, the SIR for pancreatic cancer was higher, at 87. [1,19] In HP patients, environmental variables can raise the chance of pancreatic cancer. The biggest extra risk factors for pancreatic cancer were smoking cigarettes and having a history of diabetes mellitus. [19] Smoking raises the risk of pancreatic cancer in people with HP by the same amount as it does in the general population (about doubling the risk), but it appears that people with HP who smoke get the disease around 20 years earlier than those without HP who smoke. [77] Despite a dearth of information on screening or prospective studies, the considerably elevated risk of pancreatic cancer associated with an HP diagnosis has prompted suggestions for screening. Based on consensus among experts at the Third International Symposium on Inherited Diseases of the Pancreas, the first set of recommendations was released in 2001. The Fourth International Symposium's revised recommendations were published in 2007. [78] Starting at age 40–45, or 10-15 years before the earliest age at which pancreatic cancer in the family first appeared, this panel advised screening for pancreatic cancer in patients with HP every one to three years, starting at that age. [79] Clinical recommendations for genetic testing and treatment of individuals with hereditary gastrointestinal cancer syndromes were released by the American College of Gastroenterology in February 2015. These suggestions were made for people with HP and other conditions where there is a high chance of acquiring hereditary pancreatic adenocarcinoma. The recommendations were:

1) surveillance for pancreatic adenocarcinoma should be of individuals who are known mutation carriers of hereditary syndromes associated with increased risk of pancreatic cancer and should be performed in experienced centers using a multidisciplinary approach and under research conditions;

2) surveillance should be performed with endoscopic ultrasound and/or pancreatic magnetic resonance imaging, starting at age 50 years, or 10 years younger than the earliest age of pancreatic cancer in the family;

3) cystic lesions of the pancreas identified during surveillance require evaluation by centers experienced in the care of these high-risk individuals, and the decision for surgical intervention should be individualized and made by a multidisciplinary team assessment. [80]

❖ **Diagnostic evaluation**

An extensive personal history to look for clinical symptoms, an extended family history to discover potential inheritance patterns, and radiographic imaging to check for evidence of acute or chronic pancreatitis are often part of the workup for HP. Endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) are two diagnostic endoscopic techniques that may be useful in assessing or treating the consequences of chronic pancreatitis as well as in comprehending the patient's pancreatobiliary architecture. [23] Idiopathic pancreatitis has frequently been incorrectly erroneously identified in HP patients. Genetic testing is available for the most prevalent causative mutations, such as those in the PRSS1, CFTR, SPINK1, and CTRC genes, in people who have symptoms and in whom HP is suspected. The factors that should be taken into account while deciding whether to offer genetic testing are listed in Table 1. [23,82,83] It is advised that genetic testing be carried out with the aid of a genetic counsellor or knowledgeable provider who can help with the results' interpretation and offer emotional and familial support. [84] Genetic testing can be useful for predicting outcomes in asymptomatic individuals when autosomal dominant or recessive mutations, such PRSS1 or CFTR, are thought to have been inherited. In a patient with a known mutation and a family history of HP, a negative test effectively rules out the diagnosis. In contrast, it is believed that a positive test in those circumstance increases the patient's lifetime chance of having HP by 80%. [85] Asymptomatic patients under the age of 16 should be individually evaluated before testing. [82,84]

Criteria for genetic testing for HP [23]

Consider when patients meet one or more of the following criteria:

- A family history of idiopathic chronic pancreatitis, recurrent acute pancreatitis, or childhood pancreatitis
- Relatives with known mutations associated with HP

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- Unexplained pancreatitis in a child
- Idiopathic chronic pancreatitis in patients <25 years old
- Recurrent acute pancreatitis of uncertain etiology
- Patients who are eligible for enrollment in approved research trials

❖ **Treatment**

Patients with HP should be managed in the same way as patients who present with pancreatitis of other etiologies. Preventative measures, medical management, and endoscopic and surgical interventions may all be appropriate for a patient with HP.

- **Prevention**

There are no certain ways to stop the onset or course of the disease when there is a genetic mutation linked to HP. Given the elevated risk, pancreatic adenocarcinoma surveillance, as previously indicated, is necessary. Advising patients and their families to stay away from environmental triggers that are known to aggravate and worsen pancreatitis and are believed to be implicated in the complex-type inheritance of HP is another crucial prophylactic measure. Since tobacco use is known to double the risk of pancreatic cancer, it should be avoided. [77] Since there is no known safe level of alcohol consumption, alcohol usage should be avoided as it is another recognised cofactor for the development of pancreatitis. Emotional stress and dietary fat are further triggers that should be avoided , however they are more difficult to manage. [19] Last but not least, each patient should get specific information about the risks and benefits of using drugs that have been linked to drug-induced pancreatitis, such as ACE inhibitors, HMG co-A reductase inhibitors, and selective serotonin reuptake inhibitors. [86]

- **Medical management**

It is recommended that exogenous pancreatic enzyme replacement come first, followed by food modification and trigger avoidance, before pain management is used as the final stage in medical care of pancreatitis. [23] Some patients' pancreatitis-related discomfort has been demonstrated to react to pancreatic enzyme replacement [87] and perhaps to antioxidant therapy. [88] Tricyclic antidepressants or gabapentin usage may be beneficial since the central nervous system and pain processing system have been identified as a mechanism of pancreatitis-related pain [89]. Moreover, despite the fact that nonsteroidal anti-inflammatory drugs are preferred over opioid analgesics for pain treatment, they may not be tolerated owing to side effects or be contraindicated due to the patient's comorbidities. Long-acting formulations are recommended over short- or intermediate-acting ones when prescribing opioid analgesics. [23] Amlodipine, octreotide, and somatostatin are not advised for use in HP since they have not been demonstrated to be effective in relieving pain in individuals with pancreatitis. [90–92]

- **Endoscopic therapy**

Endoscopy, like other types of pancreatitis, can be quite effective in treating HP's aftereffects as well as discomfort. In patients with chronic pancreatitis, endoscopic decompression of blocked pancreatic ducts caused by strictures or stones has been demonstrated to be related with long-term pain alleviation, with the majority of patients (76 percent in the 2002 research) effectively avoiding surgical surgery. [93,94] This result was confirmed in a group of 42 kids who received therapeutic ERCP; 64% of them claimed total pain relief and 81 % reported lessened stomach discomfort. Notably, mild to moderate post-ERCP pancreatitis or cholangitis were seen in 17% of these kids who had ERCP. [95] The effectiveness of therapeutic ERCP in a group of HP patients was assessed in 2010. Following ERCP, these individuals' levels of discomfort, narcotic usage, and hospitalizations were shown to have dramatically decreased throughout the course of their up to 39-year follow-up. Additionally, it was discovered that 12 of the patients required surgical resection at some point; yet, 92% of these patients still required endoscopic intervention following the operation. [96] Whether endoscopic care is recommended over surgical therapy in HP has been up for dispute. In 87 individuals with HP, a 2013 review compared endoscopic and surgical treatments. Ceppa et al. discovered that surgical therapy had longer pain-free intervals between sessions than endoscopic therapy. Age, comorbidities, the focality of the pancreatic lesion, and safety profiles were all things that needed to be taken into account when choosing one intervention over the other, therefore it was believed that the choice was complicated. [97] A 2015 Cochrane

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Review of three randomised controlled studies found that surgical surgery provided better long-term pain alleviation than endoscopic intervention. [98] In their interventional recommendations for kids with HP, another group advocated a step-up treatment that involved early ERCP and, if that failed, surgery. [99] According to our observations, therapeutic endoscopy should be taken into account as a significant first therapy option for patients with HP, but it must be tailored to the particular patient and carried out by skilled endoscopists.

- **Surgical therapy**

Operative care of pancreatic necrosis or for draining of pancreatic cysts may be necessary in addition to decompression of clogged pancreatic ducts. Partial pancreatectomy, complete pancreatectomy by itself, or total pancreatectomy combined with islet cell autotransplantation are all surgical alternatives for the treatment of these disorders as well as the prevention of pancreatic cancer. In addition to being age dependant, with younger patients having higher success rates, the reduction of pain and narcotic reliance following pancreatectomy and maintenance of islet cell function following autotransplantation have only been demonstrated to be somewhat successful. [100,101] An irreversible treatment, pancreatectomy with islet cell autotransplantation condemns the patient to a lifetime of exogenous pancreatic enzyme replacement and a substantial chance of developing insulin dependency over time. Therefore, before deciding to seek surgical resection, a multidisciplinary team must do a thorough risk-benefit analysis that is tailored to the patient. While there is still a large amount of islet cell mass to support a successful graft, it is best to investigate auto-islet cell transplantation early. More precise standards would make it easier for healthcare professionals to decide which patients, in which circumstances, might benefit from pancreatectomy with or without islet cell autotransplantation.

❖ MANAGEMENT DILEMMAS IN HEREDITARY PANCREATITIS

Three questions are frequently asked when confronted with a patient or family who has been diagnosed with HP. Firstly, what can be done about the patient with pancreatitis Secondly, are other relatives likely to be affected Thirdly, what can be done to reduce the risk of cancer.

1) Management of the pancreatitis

In individuals with HP, no special medical treatments are indicated. Acute pancreatitis requires the same treatment as sporadic pancreatitis, namely rehydration, analgesics, and cautious monitoring. Although severe necrotizing pancreatitis is uncommon in HP, pseudocysts appear to be very prevalent. Antioxidant treatment has been suggested as a way to avoid acute episodes, however there is no evidence to support this and it is not recommended. Chronic pancreatitis should be treated in the same way as any other patient would. It's probable that enzyme supplements and analgesics may be required. If diabetes mellitus develops, insulin treatment will very certainly be required. Complications such as a pseudocyst, biliary blockage, or duodenal obstruction require surgical treatment. A complete pancreatectomy should be considered in elderly individuals who require surgery to eliminate the cancer risk.

2) Genetic counselling of relatives

Relatives should be informed that, while the majority of HP cases are discovered by the age of 18, the illness may not appear until the age of 30 or later. Genetic testing offers no benefit to these unaffected people, and it should be avoided. Unaffected (non-carrier) persons and unaffected carriers have no higher risk of getting cancer since they do not have pancreatitis.

3) Screening of hereditary pancreatitis patients for cancer

Because people with this illness have a 53-fold greater risk of pancreatic cancer, with a cumulative risk of 40% by the age of 70, screening would seem to be necessary. Unfortunately, there is no effective screening test. The sensitivity and specificity of tumour marker measurements, endoscopic methods, and radiographic imaging are insufficient for early diagnosis. On a backdrop of chronic pancreatitis, tumours are very difficult to identify. As a result, molecular-based techniques are anticipated to provide the greatest chances for screening these high-risk individuals for pancreatic ductal adenocarcinoma [33]. It has been recommended that any screening programme should require the banking of blood and pancreatic juice samples, as well as endoscopic ultrasonography imaging of the pancreas [34]. EUROPAC has devised one such methodology for the secondary screening of HP patients (European Registry of Hereditary Pancreatitis and Pancreatic Cancer). Affected persons over the age of 30 are

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provided imaging by CT and endoscopic ultrasonography (EUS), followed by genetic analysis of pancreatic juice acquired at ERCP for K-ras mutations, as part of a research programme exclusively. Patients who test negative for K-ras have their pancreatic juice CT, EUS, and K-ras tests repeated every three years. If positive, these individuals may be at risk for pancreatic ductal carcinoma, and an ERCP brushing of the pancreatic duct should be attempted to acquire cells for cytology. The most effective prophylactic therapy in these individuals would be a complete pancreatectomy, however this is a high-morbidity procedure with a high risk of diabetes. Certainly, every patient with HP who requires surgery for symptom alleviation and is above the age of 30 should get a complete pancreatectomy rather than a less invasive treatment to eliminate the cancer risk. This is not recommended in healthy people unless there is significant evidence of cellular atypia or a localised abnormality that might indicate malignancy.

❖ **Prognosis**

In comparison to the general population, patients with HP without pancreatic cancer do not have a higher death rate. However, pancreatic adenocarcinoma often manifests in HP patients 20 years sooner than in the general population, which leads to an earlier and higher death rate. [77] However, because of their symptoms and the frequent need for hospitalizations and procedures, patients frequently have a markedly diminished quality of life.

II. CONCLUSION

Hereditary pancreatitis is an interesting disorder that has revealed fresh information about pancreatitis pathogenesis. However, many concerns remain unsolved, particularly in regards to how these mutations connect to pancreatitis and cancer. Patients with this condition should be managed by a group of skilled pancreatic experts who can also give genetic counselling. If therapeutic options are to be improved and genetic research to be pursued, patients must be registered with one of the big Hereditary Pancreatitis Registries.

Acute, recurring acute, and chronic pancreatitis can occasionally be caused by HP. Since the illness was originally reported in 1952, our understanding of it has substantially expanded. Genetic testing may now detect a number of genetic abnormalities in the genes PRSS1, CFTR, SPINK1, and CTRC that are related to the improper activation of digestive enzymes in the pancreas and have been linked to HP development. Since the introduction and growing usage of next-generation sequencing, mutations continue to be found. However, it is frequently the interplay between genes and environmental variables that causes clinical pancreatitis. The mechanism of illness development by these mutations is complicated and only poorly understood.

Therefore, it is crucial for treatment to advise patients with HP to stay away from drugs and triggers that are known to aggravate pancreatitis, such alcohol, smoke, and a high-fat diet. Similar problems to those associated with other types of chronic pancreatitis affect people with HP, including pain, blockage brought on by strictures and stones, cysts, and exocrine and endocrine insufficiency. HP differs from other types of pancreatitis in that it begins sooner and has a much higher chance of developing pancreatic cancer. It is believed that as the distinct types of HP are more clearly defined and our knowledge of their unique symptoms increases, we will be able to provide each patient with the optimal therapy more quickly.

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