original article

Wien Klin Wochenschr
https://doi.org/10.1007/s00508-021-01869-0

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Hereditary pancreatitis in childhood: course of disease and complications

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Received: 6 October 2020 / Accepted: 31 March 2021

Summary
Background Hereditary pancreatitis is rare. Pain therapy for juvenile symptom onset, child development and the risk of pancreatic carcinoma in adulthood must be considered.
Patients, material and methods Data from a cohort of 11 patients with disease onset in childhood (<16 years) were analyzed retrospectively. The gene encoding cationic trypsinogen (PRSS1), serine protease inhibitor Kazal type 1 (*SPINK1*) and cystic fibrosis transmembrane conductance regulator (*CFTR*) genes were investigated as genetic factors. Treatment concept and complications were registered. Prognosis, treatment success and quality of life were objectified using the chronic pancreatitis prognosis score and a standardized questionnaire (KIDSCREEN-10 index).
Results The mean age of symptom onset was 7.5 ± 4.2 years. The *PRSS1* and *SPINK1* mutations each occurred with 36.4%, 3 patients had a pancreas divisum and 2 a long common channel. The course of pancreatitis was obstructive in 90.9%. Exocrine pancreatic insufficiency occurred in seven patients so far (mean age 12.5 years). Stenting was performed in 72.7% and 18.2% needed pancreatic surgery. Currently the chronic prognosis score is on average 7.5 points, pain on numerical rating scale 0 (no pain). The mean KIDSCREEN-T score of 66.9 confirms a very good quality of life.
Conclusion Patients with genetically caused chronic pancreatitis are rare. Their care ranges from pain therapy in childhood and adolescence to questions concerning family planning and pancreatic cancer prevention from mid-adulthood onward. The disease is challenging for the interdisciplinary cooperation. We found the step-up strategy to be a good option for pain therapy. A national registry monitored by scientific societies with active recruitment for screening examinations will further improve and ensure care in the long term.

Keywords Juvenile pancreatitis · Chronic pancreatitis · Genetic pancreatitis · PRSS1 · Pancreatic cancer

Introduction

Hereditary pancreatitis (HP) is a rare disease that begins in childhood and is marked by recurrent or persistent pain as an expression of chronic pancreatitis [1–3]. Mutations in the gene encoding cationic trypsinogen (*PRSS1*) are an established cause of HP [1, 2, 4]. The disease is marked by autosomal dominant inheritance with incomplete penetrance [2, 4]. Mutations in the serine protease inhibitor Kazal type 1 (*SPINK1*) and cystic fibrosis transmembrane conductance regulator (*CFTR*) genes also appear to exert a predisposing effect [4, 5]. Despite the onset of disease in adolescent age and its familial incidence, mutations are not found in all patients [2]; however,

This study is based on the master's thesis (master's course in human medicine) of Regina Prommer.

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Published online: 28 April 2021

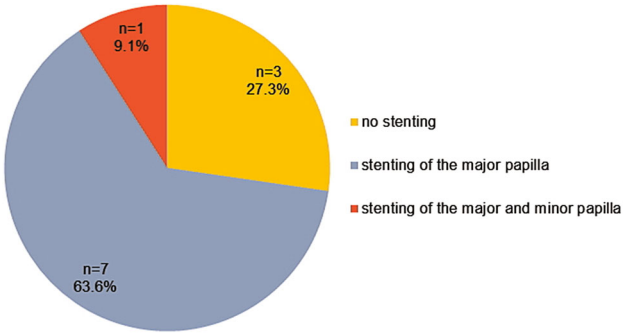

Fig. 1 Stent treatment in the herediatry pancreatitis (HP) population: In seven children the pancreatic duct was stented via the major papilla, and in one child (with pancreas divisum) through the minor and major papilla. There was no indication for a stent treatment in three patients

asymptomatic mutation carriers are also known to exist [4]. In the course of the disease the patient may develop exocrine pancreatic insufficiency (EPI) or pancreoprive diabetes mellitus, and the disease may favor carcinogenesis [2, 3].

In the present study, we reviewed clinical symptoms, child development, pancreatic function and the occurrence of complications in the course of the disease. In order to counteract deficiency symptoms and late effects of diabetes early, and because the risk of pancreatic cancer in these patients is higher than it is in the general population [2, 6, 7], we suggest the establishment of a national registry and a monitoring program.

Patients, material and methods

Laboratory data, imaging studies, interventions and operations were analyzed retrospectively in a cohort of consecutive patients with HP and primary disease onset in childhood (<16 years). The study group consisted of 11 patients, of whom 4 were male and 7 were female. The *PRSS1, SPINK1* and *CFTR* genes were investigated as genetic factors. The clinical course of the disease is described and child development was investigated in terms of percentiles or body mass index (BMI). Pancreatic function was determined with the aid of fecal pancreatic elastase and glycosylated hemoglobin (HbA1c). The treatment concept (conservative or endoscopic or surgical drainage of the pancreatic duct) and the complications observed in the course of disease were registered. We used a step-up strategy from conservative treatment to endoscopic or surgical drainage when the less invasive procedure was clinically ineffective [8]. The chronic pancreatitis prognosis score (COPPS) allows an objective assessment of the success of treatment and the prognosis of disease [9]. Furthermore, all patients between the ages of 8 and 18 years completed a standardized health questionnaire for children and adolescents (KIDSCREEN-10 index) at the time of the last follow-up investigation [10]. This questionnaire reflects the quality of life in children with HP.

The statistical analysis was carried out using descriptive statistics. The COPPS was calculated from laboratory data from the last follow-up investigation The questionnaire for children and adolescents (8–18 years) was evaluated with the associated evaluation tool and shown as KIDSCREEN-T score.

Results

The total follow-up period comprised 136 patient years. The patients' mean age at the onset of symptoms was 7.5 ± 4.2 years. In 9 of the 11 children with HP the symptoms occurred within the first 10 years of life. In 4 children the symptoms occurred even before the age of 6 years. Only 2 children developed their preliminary symptoms when they were older than 10 years. In patients with a *PRSS1* mutation, the mean age at disease onset was 3 years in those with maternal inheritance of the disease, and 9 years in those with paternal inheritance. In other words, we were able to confirm an association between early disease onset and maternal inheritance of *PRSS1*, as reported in a previous study [11]. In our patients, mutations of the *PRSS1* and *SPINK1* genes were found in four patients each. In one case we found a compound heterozygous *CFTR* mutation, and in two patients we detected none of the three investigated mutations despite typical clinical symptoms and familial clustering. At the time of diagnosis (positive genetic testing for mutations in the genes *PRSS1, SPINK1* and/or *CFTR*) the patients' mean age was 12.1 ± 7.2 years (9 of 11 patients). We noted a mean interval of 3.9 ± 5.1 years from the onset of disease to the diagnosis. The diagnosis was established within 12 months after the onset of disease in 4 children, and after more than 5 years in 4 other children.

Endoscopic retrograde cholangiopancreaticography (ERCP) or magnetic resonance cholangiopancreaticography (MRCP) revealed a pancreas divisum in three children. The ERCP showed a long common channel (>5 mm) in two children [12]. As regards complications of the disease, during an acute flare of pancreatitis we found ascites in four children and necrosis in three and two children had partial atelectasis of the lungs and pleural effusions. Paralytic ileus, pleural fistula and peritonitis was noted in one patient each. Pseudocysts requiring intervention were observed in four patients, and with no need for intervention in a further four patients. Two patients had already undergone a cholecystectomy.

The time period from disease onset to the first invasive intervention (ERCP or operation) was on average 10.1 ± 19.0 months. The patients' mean age at the first intervention was 8.3 ± 4.0 years.

In our group 10 patients had an obstructive type of HP, whereas 1 patient had chronic calcifying pancreatitis without stenosis and significant dilation of the

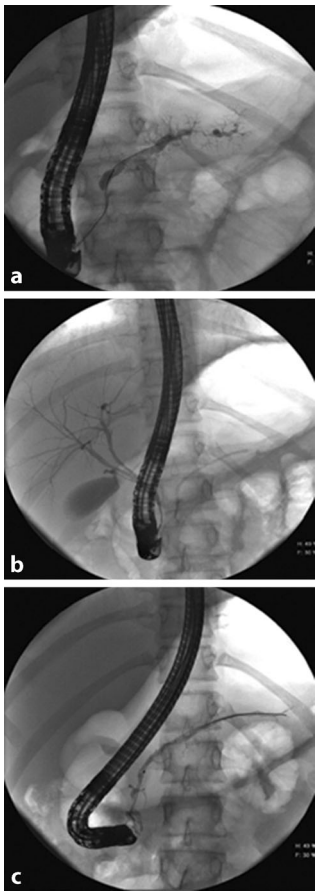

Fig. 2 Endoscopic retrograde cholangiopancreaticography (ERCP) of a 12-year-old female patient with cationic trypsinogen (*PRSS1*) mutation. **a** Before stent treatment, the pancreatic duct was irregularly dilated due to severe stenoses, **b** during the 1-year stenting program and **c** after stent treatment, a straight and narrow pancreatic duct was achieved

major duct, 9 children underwent a sphincterotomy of the pancreatic sphincter at the ERCP, twice combined with a biliary sphincterotomy and once combined with a papillotomy of the minor papilla. In one case we were unable to perform any intervention on the papilla due to duodenal stenosis. In another patient with a long common channel, we could only perform a biliary sphincterotomy but no pancreatic sphincterotomy. In one case we established the indication for extracorporeal shock wave lithotripsy (ESWL) because of pronounced pancreaticolithiasis.

Stenting was performed in eight cases (Fig. 1). The mean duration of stent treatment was 11.5 ± 6.5 months; the stent was changed every 3–4 months. Five children completed a 1-year stenting program with a mean duration of 13.7 ± 3.3 months (Fig. 2), while 3 other patients completed a short-term stenting program. The reasons for the short-term stent were as follows: pain relief and a normal pancreaticography in one case, pancreaticolithiasis that could not be treated by endoscopy in the second case, and transpapillary drainage of a pseudocyst with ductal communication in the third case. As the ERCP was unsuccessful in two children, once due to duodenal stenosis with increasing number as well as intensity of relapses and the other time in a patient with a long common channel because of cystic dilatation of the pancreatic duct in the caput with calcification into the cauda and the impossibility of probing of a pancreatic duct stenosis, we decided to perform surgery (pancreaticojejunostomy) as the next option of the step-up strategy. In both cases, ERCP was performed only once, with no previous stenting treatment.

Of our patients, 7 children developed EPI at the average age of 12.5 ± 8.4 years. A fecal pancreatic elastase level < 200 µg/g stool was used as the cut-off value. All of the patients had < 100 µg/g at the onset of disease, and 4 of them had < 50 µg/g. In 5 children EPI occurred before the age of 10 years. Pancreoprive diabetes mellitus (type IIIc) was not observed in any case so far. To date, no patient has developed pancreatic cancer.

Longitudinal analysis of child development based on percentiles of BMI showed that at disease onset 2 of the 11 patients were below the 10% and 1 patient was below the 25% percentile, but none of the 10 patients at the last follow-up investigation was below the 25% percentile. We attribute this to the fact that active interventions such as the administration of pancreatic enzymes for EPI, patient education, stenting and surgery helped to avoid or improve underweight.

At the last follow-up investigation (10 patients), the COPPS (analogous to the Child-Pugh score for chronic liver disease) was on average 7.5 points (COPPS stage B = 7–9 points, range 5–15 points) and the patients reported an average score of 0 (no pain) on the numerical rating scale (NRS) for pain. Thus, the step-up strategy proved to be the right approach. The mean KIDSCREEN-T score of 66.9 was also satisfactory, indicating very good quality of life (the mean score in healthy persons of this age group is 54.3).

Discussion

Our population of 11 patients with genetic pancreatitis was analyzed in terms of epidemiology, etiology, clinical symptoms and treatment. The following considerations and comparisons were applied: a genetic investigation is recommended in patients with initial symptoms of pancreatitis if the index case is young (below 30 years of age) or has a positive family history. If the investigation reveals a mutation linked to HP, we recommend a family screening. A simple blood test can be used to identify persons with the same gene mutation (asymptomatic mutation carriers or those with mild symptoms). Surveillance of asymptomatic or oligosymptomatic persons with HP mutations would also be advisable because pancreatic carcinomas are found in relatively young persons with no or little pain and no clinical abnormalities.

According to Ballard et al. patients with pancreatitis due to genetic causes have a pancreas divisum significantly more often (27%) [13]. We also observed this association in our patients with HP. Bertin et al. demonstrated this association especially with respect to *CFTR* mutations and polymorphisms [14]. Protective polymorphisms and mutations may also play a role. With respect to *CFTR* mutations and pancreas divisum, Nicholson et al. stated that a pancreas divisum may also exert a protective effect on pancreatic function [15]. The additional orifice via the minor papilla into the duodenum may permit better drainage of pancreatic secretion, which is altered by the mutation. Only one of our patients had a *CFTR* mutation (compound heterozygous) with no pancreas divisum and no clinical sign of EPI.

We still do not know the underlying factors that cause one patient to experience the onset of HP, whereas another patient with an identical *PRSS1* mutation remains an asymptomatic carrier. Cofactors such as pancreas divisum or a long common channel and hitherto unknown pathogenic and protective mutations/polymorphisms appear to contribute to the phenotypic expression of the disease. In our population, two female patients with *PRSS1* mutations had symptomatic disease onset in childhood, whereas their family members with the identical *PRSS1* mutation (in one case the father and in the other case the father as well as the brother) were asymptomatic *PRSS1* mutation carriers. This raises the question as to whether the asymptomatic *PRSS1* status is more common in males. On the contrary, Shelton et al. noted men as silent *PRSS1* mutation carriers only in 39% of the asymptomatic cases [7]. It appears that complex multigenetic factors rather than a simple interaction between genes and the environment are responsible for the phenotypic manifestation of HP.

Consistent to our step-up therapy concept, the indications for surgery are given if endoscopic interventions remain unsuccessful. In these cases, surgery is inevitable to ensure pain relief as well as good child development and quality of life. Longitudinal pancreaticojejunostomy as surgical approach proved to be safe and effective in our patients who had undergone surgery. Prophylactic pancreatectomy resolves the increased risk of pancreatic ductal adenocarcinoma, but despite the high-risk situation, currently we do not favor this precautionary surgery in patients with HP.

The surveillance of HP patients in the period of transition from childhood to adolescence and adulthood is a critical issue. Following successful treatment with stenting or surgery, regular controls may be easily omitted because the patient is free of pain. Therefore, we emphasize the importance of adequate and thorough education of patients. Patients should understand the reason for surveillance, attend the investigations and minimize avoidable risk factors.

The risk of pancreatic cancer is higher than it is in the normal population, but the actual level of risk is unclear. While Shelton et al. noted a cumulative risk of 7.2% at the age of 70 years, older studies reported a cancer risk of about 40% (which increases to about 75% in cases of paternal inheritance) [2, 6, 7, 11]. In this context it should be noted that the number of patients with *PRSS1* mutation varies in the studies. Shelton et al. included asymptomatic cases in their analysis. Patients should be urgently advised to avoid alcohol and smoking because these exogenous toxins may exert a harmful effect on carcinogenesis.

HP registries and databases exist in Europe. Their purpose is to collect information about the genetic basis of the disease, its development and the risk of pancreatic cancer. The English European registry of hereditary pancreatitis and familial pancreatic cancer (EUROPAC) registry is one such registry for HP [2]. In 2009 Rebours et al. published the French HP registry [11]. CFTR-France is another database that contains CFTR variations (genotypes, phenotypes, sequence variations); it also includes the phenotype with pancreatitis [16]. In 2018 Shelton et al. published mortality rates and the incidence of pancreatic cancer in a large US American population [7]. We are striving to establish an Austrian HP registry. By including asymptomatic cases, we hope to be able to analyze associations between genotypes and phenotypes. In following up patients, the registry will focus on prevention so that in the case of cancer appropriate measures can be instituted as early as possible. By doing so, we hope to provide curative treatment and improve the prognosis of the disease. Patients with undetected mutations should also be included in the registry along with the collection of whole blood samples. Thus, the patients can be tested again when a new mutation is discovered. Persons should be actively invited to participate in the registry for the purpose of monitoring. Yearly control investigations, including clinical examinations, laboratory tests, endosonography or magnetic resonance imaging (MRI)/MRCP should be performed at one center in each province of the country. A HP registry will also make it possible to recruit patients as candidates for studies focused on new treatment options.

Acknowledgements Sincere thanks are owed to Wolfgang Pumberger, the former head of the department of pediatric surgery at the Kepler University Hospital in Linz, for the development of the step-up concept for the treatment of hereditary pancreatitis in children.

Author Contribution This draft of the manuscript was written by Regina Prommer and Rainer Schöfl commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest R. Prommer, M. Kienbauer, S. Kargl and R. Schöfl declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. This analysis of our cohort of patients with HP was approved by the ethics committee of the Land Oberösterreich (State of Upper Austria 1124/2019, 22 July 2019) and by the ethics committee of the hospitals of the Sisters of Charity and the Brothers of Charity Linz (40/19, 29 July 2019). Informed consent was obtained from all patients who participated in the last follow-up investigation (prospective part) or their legal representatives. According to the ethics committees, no declaration of consent was required for purely retrospective data analysis.

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