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Analysis of Pediatric Pancreatitis (APPLE Trial): Pre-Study Protocol of a Multinational Prospective Clinical Trial

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What Is Known

- Increased number of acute pancreatitis (AP) in children.
- Small amount of prospective clinical trials in children suffering from pancreatitis.
- No running worldwide prospective clinical trials for pancreatitis in children.

What Is New

- A multinational prospective clinical trial is registered and open to all centers.
- This is the first worldwide study tracking earlier episodes (APPLE-R) of pancreatitis.
- This is the first worldwide study tracking ongoing episodes (APPLE-P) of pancreatitis.

Key Words
Pediatric pancreatitis · Acute pancreatitis · Genetic mutations · Evidence-based medicine

Abstract

Background: Single-centered studies show increased number of acute pancreatitis (AP) in children. Here, the Pediatric Section of the Hungarian Pancreatic Study Group introduces an international observational clinical trial (APPLE) to collect a critical mass of clinical data and biomedical research samples in a uniform prospective manner. ***Summary:*** The APPLE-R is for patients under 18 years of age with a history of pancreatitis. The study primarily provides information on possible genetic variants behind the disease and their impact on the prognosis. The APPLE-P is for patients under 18 years of age with a diagnosis of AP. Children with AP diagnosed based on the fulfillment of '2 out of 3' of the Atlanta

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criteria will be selected. This subtrial requests detailed information from the medical history, etiology, complains and symptoms, physical examinations, laboratory parameters, imaging, immediate therapy at admission and complications of the disease. The APPLE trial has been registered at the ISRCTN registry and has received the relevant ethical approval. The study is open for all pediatric centers throughout the world. ***Key Message:*** This is the first worldwide study tracking earlier (APPLE-R) and ongoing episodes (APPLE-P) of pancreatitis.

Introduction

In the past few years, studies have showed an increased number of AP in children [1–8]. Based on the latest epidemiology report, there were over 50,000 new cases in the United States from 2000 to 2009 [7]. The fact that the incidence of AP in adults is 4.8–38 per 100,000 and is 3.6–13.2 per 100,000 in children suggests that AP in children is as common as it is in adults [8]. It is almost needless to say that children are not 'small adults'; however, the suggestions for the management of AP in children are mostly based on clinical trials performed on adults [9, 10]. Analyzing the available PubMed data (fig. 1), we can assume that there are around 10 times more articles available for AP in adults than there is for children. Therefore, it is not surprising that the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) highlighted the crucial necessity of multicenter prospective studies to better understand AP in children [10].

The Hungarian Pancreatic Study Group (HPSG) was established in 2011 in order to improve the care of patients suffering from pancreatic diseases. To achieve our aims we (i) developed an electronic data registry and biobank for patients (www.pancreas.hu), (ii) published the currently available evidence-based medicine guidelines [9, 11–13], (iii) established specific study sessions including the pediatric section and (iv) organized multicentre clinical trials [14, 15].

Here, the Pediatric Session of HPSG introduces an international observational clinical trial (APPLE) to collect a critical mass of clinical data and biomedical research samples in a uniform prospective manner. Importantly, the study protocol is suitable for tracking both ongoing (APPLE-P) and earlier episodes (APPLE-R) of pancreatitis.

Methods

Preliminary Settings

The study has been initiated and drafted by the HPSG. The protocols have been introduced in our latest international meeting held in Szeged in November 2014 (http://pancreas.hu/sites/info/files/conferences/ALPD2014-Program.pdf), where expert pediatric pancreatologists attended. Moreover, around 100 clinicians (60 Hungarians and 40 international [from 9 different countries]) and investigators attended. Experts provided input on the design and output of the study; changes suggested by the consensus were incorporated into the study. The study has been discussed and accepted by the scientific committee of the International Association of Pancreatology; therefore, it is running under the auspices of HPSG and International Association of Pancreatology.

Ethical Issues

The studies have received the relevant ethical approval (No. ad.52499-3/2014) issued by the National Hungarian Ethical Authority (ETT TUKEB). Study management will strictly follow the Ethical Guidelines for Observational Studies. Single sites will be required to get approval from the ethics committees at their institutions prior to participation.

Trial Registration

The APPLE trial has been registered at the ISRCTN registry (ISRCTN89664974) which is a primary clinical trial registry recognized by WHO and ICMJE that accepts all clinical research studies, providing content validation and curation and the unique identification number necessary for publication.

Patients and Centers Involved into the Trial

The APPLE trial is divided into 2 subtrials.

The APPLE-R is for patients under 18 years of age with a history of pancreatitis. The aim of APPLE-R is to collect patients suffering from any kind of pancreatitis AP, acute recurrent pancreatitis and chronic pancreatitis. Approximately, 800 patients are expected to be collected within 3 years.

The APPLE-P is for patients under 18 years of age with currently diagnosed ongoing AP. Approximately, 300 patients are expected to be enrolled within 3 years. Patients with AP diagnosed based on the fulfillment of '2 out of 3' of the criteria [9, 10] will be selected.

Centers throughout the world are welcome to participate in the APPLE trial. 'Online Call for Centers' will be available at http://www.pancreas.hu/en/studies/apple. Completion of the 'LETTER OF INTENT' form will be mandatory for registering participation of each institution. HPSG will acknowledge receipt of the 'LETTER OF INTENT' form and will contact centers providing them with additional study information.

Protocol for Prospective Electronic Data Collection

Both the APPLE-R and APPLE-P subtrials have a questionnaire style data collection method. The forms are available on the web system http://www.pancreas.hu/en/studies/apple. The patients and parents have to be informed accordingly. The 'informed consent form' needs to be signed and the relevant 'Questionnaire' needs to be filled out. Four quality control points are established. First, the local clinical research assistant needs to upload the data electronically and confirm that the data are equivalent with the

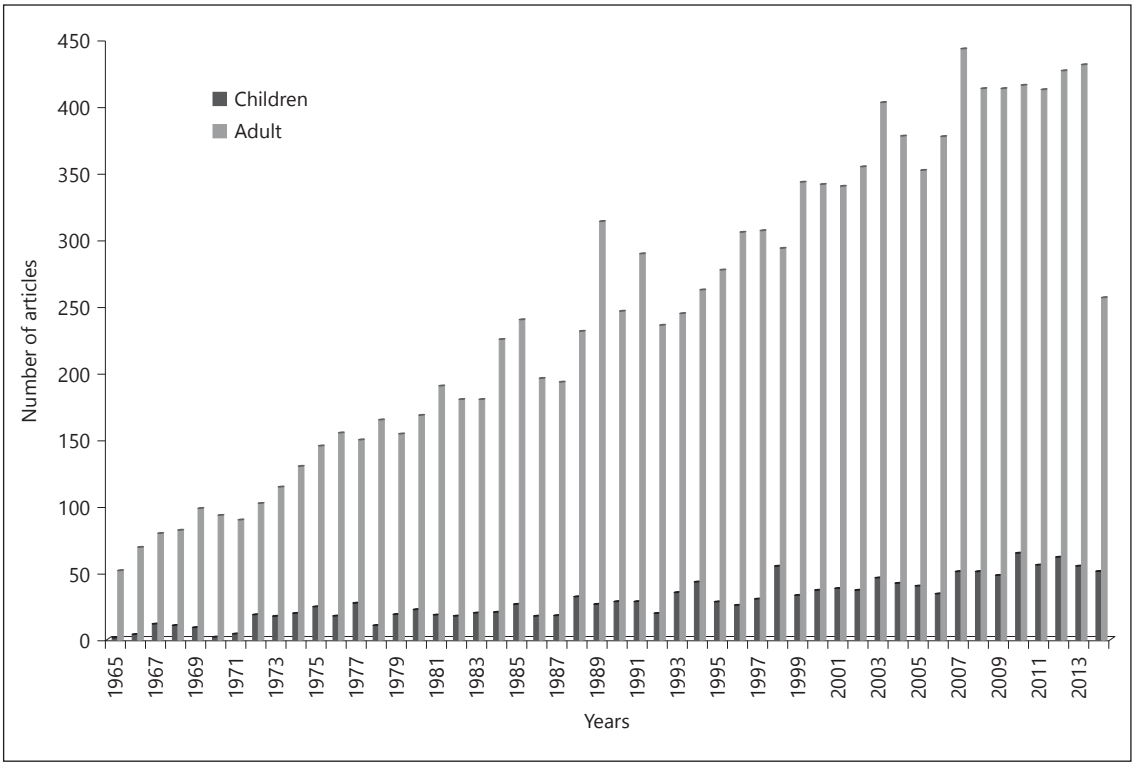

Fig. 1. Annual distribution of available papers in AP in adults and children. Results of PubMed searching for 'acute pancreatitis, adult' and 'acute pancreatitis, children' in the last 50 years are shown.

hard copy. Second, the local institutional principal investigator (who has to have a medical doctoral degree) needs to recheck the uploaded data and confirm the validity and accuracy. Third, the central data administrator, who is based at the headquarters of HPSG, controls the accuracy and finally, the trial leader goes through the details. Patients with inadequate or insufficient data will be excluded.

Protocol for Blood Collection and Genetic Testing

Whole blood (6 ml) needs to be collected in EDTA tubes and stored at –20°C until delivery to the biobank in Szeged. Genomic DNA will be isolated and genetic analyses of the cationic trypsinogen *(PRSS1)* [16–19], chymotrypsin C *(CTRC)* [20, 21], cystic fibrosis transmembrane conductance regulator *(CFTR)* [22], serine peptidase inhibitor Kazal type 1 *(SPINK1)* [23, 24], carboxypeptidase A1 *(CPA1)* [25] and carboxyl-ester lipase *(CEL)* [26] will be performed. In order to detect the most common mutations concerning *PRSS1* (p.A16V, p.N29I, p.R122C and p.R122H) exon-2 and exon-3, concerning *CPA1* mutations (p.V251M, p.N256K, p.Y308H and p.R382W) exon-7, exon-8 and exon-10, concerning *SPINK1* (p.N34S and c.194+2T>C) exon-3, concerning *CTRC* (p.G60G, p.V235I, p.R254W and p.K247_R254del) exon-3 and exon-7, concerning *CFTR* (p.R117H and p.F508del) exon-4 and exon-11 and concerning *CEL* all exons will be sequenced. This will help to understand the complex interaction of genetic variants in pancreatitis patients and identify risk constellations. Please NOTE that control samples have to be provided for the genetic testing by each center. Ages and gender (F/M) details have to be given.

Details of the APPLE-R Subtrial

Patients who had acute episode(s) earlier can be involved in the APPLE-R study. It is important that the first pancreatitis episode should be before the age of 18 years. The study primarily provides information on possible genetic variants behind the disease and their impact on the prognosis. The 'APPLE-R Questionnaire' requests details from the medical history and etiology of the disease. For details see online supplementary document 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000441353) or the 'APPLE-R FORM A' on the trial web site http://www.pancreas.hu/en/studies/apple.

Please NOTE, if the patient has been involved in earlier genetic studies and the relevant gene mutations have been reported it has to be clearly mentioned in the question no. 4 at the APPLE-R FORM A. It is crucially important to avoid second reporting of a scientific finding.

Details of the APPLE-P Subtrial

Newly diagnosed patients who are currently in active stage and under the age of 18 years can be involved in the APPLE-P study. Since this subtrial primarily aims to understand the development of the disease and to identify the early risk factors, detailed examination at the first appearance (most probably at the ER unit) of the patient is crucial and cannot be made up for later. The 'APPLE-P Questionnaire' requests detailed information from the medical history, etiology, complains and symptoms, physical examinations, laboratory parameters, imaging, immediate therapy at admission and complications of the disease. For details see online

supplementary document 2 or the 'APPLE-P FORM A' on the trial web site http://www.pancreas.hu/en/studies/apple. To follow the development of the disease, detailed information on the patient's state, examinations, therapy and complications is requested during every day of hospitalization. For details see online supplementary document 3 or the 'APPLE-P FORM B' on the trial web site http://www.pancreas.hu/en/studies/apple.

Statistical Analyses

Statistical analysis will be carried out by data mining methods. The applied method will be determined based on the main characteristics of the collected data, and the most suitable method – or method combination – will be chosen. Generally, for the APPLE-P study, first we will analyze the associations between all the parameters (either individual or group parameters) collected during the study and the severity of pancreatitis. After that, we will determine the level of association. After that, the following data mining methods are being contemplated: logistic regression, discriminant analysis, random forest analysis, decision tree and cluster analysis. Receiver operating characteristic analysis and/or confusion matrix will be performed to evaluate the predictive power of the classification algorithm.

Expected Results

APPLE-R study will help to understand the complex interaction of genetic variants in pancreatitis patients, whereas the APPLE-P will provide detailed information concerning the development and the course of pediatric pancreatitis. We hope that we will be able to provide a simple, pediatric-specific, clinical scoring system that can stratify patients with AP according to their risk for severe disease course.

Authorship Policy

In order to give appropriate credit to each investigator/center, we will use standardized authorship policy. At least 5 patients are required for a co-authorship. All other investigators/contributors who do not meet the criteria for authorship will be listed in an 'Acknowledgments' section, for example, those who provide pure technical help or a department chair who provided only general support.

Discussion

Inflammatory disorders of the exocrine pancreas are among the most challenging and expensive gastroenterological disorders in adults. While acute inflammation of the gland can lead to severe disease with a mortality rate of 30–50%, the chronic form is usually not life-threatening but can diminish the patients' quality of life and can promote the development of pancreatic cancer [27]. Although the incidence of AP in children is only 2–3 times less than in adults, our knowledge in pediatric AP is very limited. The current situation is difficult for the following reasons: (i) there is a limited number of scientists working in the field, genetic tests for pancreatic patients are unavailable or testing is not organized at the national level in most of the countries, (ii) there is a big and unacceptable high difference in disease recognition and outcome among the countries, (iii) limited number of biobanks or patient registers are available; those that exist are mostly organized on national levels with no links to international consortia and (iv) funding is often refused because of the low importance. Therefore, multinational efforts are crucially needed [28].

There are clear evidences that the disease development in children is different than in adults. For example, the etiology of pediatric AP compared to adults is more diverse. The most common etiological factors in children are idiopathic and biliary causes, followed by trauma, systemic disease, medication, viral infections, metabolic disorders, diabetes mellitus, hypertryglyceridemia and hypercalcemia [3, 4, 6]. No specific etiological factor was found in 13–34% of all pediatric AP cases [3–6, 29]. Results from the Danish population-based cohort study showed that genetic mutations that elevate the risk of pancreatitis can occur in 32% of idiopathic acute cases in young patients [30]. Early onset and/or recurrent episodes of AP can further elevate the possibility of genetic alterations [8, 30, 31]. The INSPPIRE consortium highlighted that the current diagnostic practice is also differ between children and adults. Trans-abdominal ultrasonography is more commonly used than CT in the initial presentation of children with AP in order to limit radiation. MRI is also more frequently performed in cases of recurrent AP or chronic pancreatitis [10]. Concerning the diagnosis, the key predicting signs in adult for pancreatitis are vomiting and nausea; however, it appears only in 74% of the cases in children [32].

Predicting the severity of pancreatitis needs to be improved in children. For adults, the Ranson criteria [33, 34], Modified Glasgow [35] and the Acute Physiology and Chronic Health Evaluation II [34, 36] score have been developed for predicting the severity. Three studies have confirmed that the above-mentioned clinical scoring systems had low sensitivity in children and cannot be used as a predictors of outcome for pediatric pancreatitis [37–39]. DeBanto et al. [40] published the first pediatric-specific AP severity score. This score requires 48 h to be completed and has not been validated in prospective studies. There is a need for an easy, simple, pediatric-specific, clinically oriented novel models to further improve predictive accuracy of severity in AP [41]. Concerning the treatment of AP in children, the situation is even worse. Almost only adult experiences are available for pediatricians to order treatment in everyday practice [9, 28].

In summary, here we propose a multinational observational clinical trial (APPLE) to collect a critical mass of clinical data from children suffering from AP in a uniform prospective manner to help fill the knowledge gap and provide simple, pediatric-specific, clinical scoring system that can stratify patients with AP on presentation. It is important to mention that after the APPLE study, we plan to design a follow-up longitudinal study for better understanding of PP.

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Disclosure Statement

All authors disclose any sponsorship or funding arrangements relating to their research and disclose any possible conflicts of interest.

Authors Contributions

P.H. initiated, whereas A.P. drafted the study. All the authors were involved in designing and discussing the study.

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