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Efficacy of group biofeedback treatment on hyperemesis gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomised controlled trial

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ABSTRACT

Introduction Hyperemesis gravidarum (HG) is a condition characterised by dehydration, electrolyte imbalance, lack of nutrition and at least 5% loss in body weight, occurring in the first half of pregnancy. The aim of this trial is to examine the efficacy of group biofeedback treatment on patients with HG with psychosomatic symptoms, which will be evaluated through the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R).

Methods and analysis In this single-blinded randomised controlled clinical trial, 68 patients with HG diagnosed with at least one psychosomatic syndrome according to DCPR-R and aged 18–40 years, will be recruited in a Chinese Maternal and Child Health Hospital. The sample will be randomised (1:1) into two arms: experimental group, which will undergo group biofeedback treatment, psycho-education and treatment as usual (TAU); and control group, which will undergo psycho-education and TAU only. The primary outcomes will be reduction of the frequency of psychosomatic syndromes, severity of nausea/vomiting, quality of life and heart rate variability. The secondary outcomes will include days of hospitalisation, repeated hospitalisation and laboratory investigations.

Ethics and dissemination This study has received ethical approval from the Nanjing Medical University (No. 2019/491, granted 22 February 2019). All participants will be required to provide written informed consent. Study outcomes will be disseminated through peer-reviewed publications and academic conferences, and used to confirm a tailored biofeedback intervention for patients with HG with psychosomatic symptoms.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2000028754).

Strengths and limitations of this study

► This is the first study to evaluate psychosomatic syndromes in patients with hyperemesis gravidarum (HG) according to the revised version of the Diagnostic Criteria for Psychosomatic Research (DCPR-R).
► This study will investigate the effect of a group biofeedback therapy on the severity of nausea/vomiting among patients with HG.
► This study will examine the effect of a group biofeedback therapy on the reduction of the frequency of psychosomatic syndromes evaluated by means of DCPR-R among patients with HG.
► Since this is a single-blind trial, the placebo effect of biofeedback in the experimental group could not be excluded.
► The severity of psychosomatic symptoms will not be assessed, since DCPR-R syndromes are conceived as categorical constructs.

BACKGROUND

Hyperemesis gravidarum (HG) is a condition characterised by dehydration, electrolyte imbalance, lack of nutrition and at least 5% loss in body weight.[1] HG rates in pregnant women range from 0.3% to 3%, and it is considered one of the most important pregnancy-related complications.[2] HG appears in the first half and can last throughout the pregnancy, although the symptoms usually resolve within 20 gestational weeks.[2] Moreover, HG usually recurs in subsequent pregnancies following an affected one in up to 81% of the cases.[3] This condition generally requires frequent visits to the emergency room and repeated hospitalisations for intravenous hydration, which severely compromise the quality of life (QoL).[4] Hospitalisation rates for HG vary between populations, such as from 1% to 2% in the USA[5] and 10.8% in Shanghai (China),[6]

whereas about the 37.6% of women admitted to hospital for HG return for a second hospitalisation during their pregnancy in Israel.[7]

The aetiology and pathogenesis of HG remain uncertain, even though they are likely to be multi-factorial, including biological, psychological and socioeconomic antecedents,[8] such as maternal endocrine disorders, hepatic abnormalities, gastrointestinal dysfunction, pituitary axis malfunction, autonomic nervous dysfunction and psychosomatic factors.[9] The complications of HG include multiple nutritional deficiencies, Wernicke's encephalopathy, oesophageal laceration, premature termination of the desired pregnancy and fear of subsequent pregnancy, preterm birth and low birth weight.[2]

The Diagnostic Criteria for Psychosomatic Research (DCPR) were developed to diagnose psychological disorders that could have a negative prognostic role in medical illnesses, but are not detectable with the use of Diagnostic and Statistical Manual of Mental Disorders (DSM)—based on traditional psychiatric criteria.[10] The DCPR have demonstrated an excellent predictive validity for psychosocial functioning and treatment outcomes in several medical settings, including oncology,[11] dermatology,[12] endocrinology,[13] cardiology,[14 15] gastroenterology[16] and immune system.[17] In 2017, a revised version of the DCPR (DCPR-R) was published.[18] To date, no study has examined the prevalence of the DCPR syndromes in HG.

Group biofeedback is a method to process in-vivo information related to psychological and physiological activities, such as muscle tension, skin temperature, heart rate, blood pressure, brain waves, for multiple patients (2–20) at the same time.[19] Its working principles include heart rate variability (HRV) biofeedback, abdominal breathing and Jacobson's muscle relaxation.[20] Biofeedback constitutes a non-invasive psychological intervention, which showed its efficacy in the treatment of asthma, chronic obstructive pulmonary disease, irritable bowel syndrome, cyclic vomiting, recurrent abdominal pain, fibromyalgia, cardiac rehabilitation, hypertension, chronic muscle pain, pregnancy induced hypertension, depression, anxiety, post-traumatic stress disorder.[21] It was also used to decrease perinatal anxiety and depression in the third trimester[22] and psychological stress during the early postpartum period.[23] To our knowledge, there is no information about the efficacy of group biofeedback on psychosomatic symptoms in the first and early second trimester of pregnancy.[24]

We propose two hypotheses in this study. First, we hypothesise that the 2-week group biofeedback therapy will reduce the frequency of psychosomatic syndromes, the severity of nausea/vomiting, and improve the HRV index and QoL of patients with HG with psychosomatic syndromes. Second, with the remission of nausea or vomiting, we hypothesise that the days of hospital admission and the number of repeated HG treatments in the experimental group will be significantly smaller, and laboratory investigations significantly better, than those reported in the control group.

METHODS
Study design
This randomised controlled trial will be single-blind, in the sense that the investigators who will perform randomisation, assessment and statistical analyses, will be blind to participants' group allocation. Change in primary outcome will be measured from baseline to 2-week postintervention, while change in secondary outcomes will be measured from baseline to 20-week follow-up. All personal data will be treated confidentially. Protocol Version 1.1, dated 1 March 2017.

Participants
Patients will be recruited at the Department of Gynecology of Changzhou Maternity and Child Healthcare Hospital affiliated with Nanjing Medical University, Changzhou, China. Approximately 190 patients with HG were hospitalised yearly at this department. We expect to recruit 68 patients diagnosed with at least one psychosomatic syndrome.

A sociodemographic interview, including information on age, previous miscarriage, gestational age when vomiting started (weeks), days of vomiting at admission, hyperemesis in a previous pregnancy, income, level of education, employment status, medical history, weight at admission, will be administered at baseline.
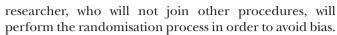
Eligibility criteria
1. Diagnosis of HG in a singleton pregnancy documented by the presence of severe vomiting (more than three times per day without any other obvious cause), an inability to maintain oral nutrition, weight loss of more than 3 kg and at least one positive ketonuria test.[2]
2. At least one psychosomatic syndrome according to the evaluation of DCPR-R system.[18]
3. No evidence of antenatal bleeding, no antibiotic treatment, H2 blockers or proton pump inhibitors in the previous month.[25]
4. Patients without any psychiatric comorbidity (schizophrenia, bipolar disorder, substance dependence, personality disorder), as ascertained from the clinical records consultation.
5. Age ranging from 18 years to 40 years old.

Exclusion criteria
Exclusion criteria include fetal anomaly, antenatal bleeding, multiple pregnancy, systemic disease, hyperthyroidism, hepatic disorders, urinary tract infections or intracranial disorders, gastrointestinal diseases, and difficulty to understand the questions and follow the instructions.

Randomisation and blinding
Participants who will be eligible in the screening phase and agree to sign the consent form, will be randomly assigned to the experimental group or control group. The random sequence numbering will be carried out by a computer program (the Random Allocation Software V.2.0), with an allocation ratio of 1:1. An independent

researcher, who will not join other procedures, will perform the randomisation process in order to avoid bias.

The researcher responsible for the assessment will be blinded to participants' group allocation. The patients will be informed that two different intervention techniques will be tested. The interventions will be scheduled at different times and days, so that participants will not have contact between groups. Data collection will be conducted by a blinded and trained researcher.

Finally, the researcher responsible for statistical analyses will be blinded too. Once the study will be concluded, this researcher will receive a dataset with all necessary data without identification of participants and groups.

Intervention

Three interventions will be performed in the two groups: group biofeedback intervention, psycho-education and treatment as usual (TAU). A nurse who received professional biofeedback training will administer the group biofeedback. The goal of this programme is to help participants to learn diaphragmatic breathing techniques, Jacobson's muscle relaxation and guided Imagery, while monitoring HRV. The intervention will include ten sessions delivered every working day in 2 weeks. Each session will last about 30–40 min, in a group setting (2–4 participants).

► Session 1: first, teach patients about the mechanism of group biofeedback, the science behind the technique, and potential benefits and outcomes of its use. Second, measure baseline HRV in 5 min time interval. Third, teach participants the slow breathing at resonance frequency about 6.5–6 breaths/min, for 10 min. Finally, guide participants how to tense and relax larger groups of muscles: (a) feet and legs; (b) stomach and chest; (c) arms and hands; (d) shoulders, back and neck; and (e) face. Muscle relaxation will last 10 min.

► Session 2: first, measure the HRV in 5 min time interval. Second, conduct the slow breathing at resonance frequency about 6 breaths/min, for 10 min. Finally, implement the progressive muscle relaxation (PMR) and body scanning to manage tension for 10 min.

► Sessions 3–5: tell the participants to do as the session 2. In addition, participants are instructed to practice resonance frequency breathing as a 10 min daily homework.

► Session 6–9: tell the participants to do as sessions 3–5. Additionally, after muscle relaxation, ask the participants to watch love, compassion and forgiveness images on the computer screen, and encourage them to enter a calm, safe, content and relaxed state through the guided imagery. This costs 10 min.

► Session 10: first, measure the HRV in 5 min time interval as the postintervention. Second, ask patients to think about three questions: 'what have you experienced during the intervention', 'what you have learned from the intervention', 'which feedback

exercise you will practice by yourself in the future'. Tell patients they can do the exercises routinely, or when they just realise that they are overly emotional or dysfunctional. Finally, repeat the three exercises for the last time.

The psycho-education includes explanations of the detrimental effect of psychosomatic symptoms on the treatment of HG, of maternal anxiety and depression on both the fetus and the infant (ie, behavioural problems, learning difficulties, psychiatric illness in the offspring and premature termination of pregnancy). In addition, participants will also be told that social interactions can help release anxiety and depression. Individual psychoeducation will be implemented only once for 30 min before each participant will be assigned either to experimental group or control group.

TAU will involve any recommendation given to the participants by their gynaecologist, including parenteral antiemetic medications, electrolyte repletion and nutritional support. Patients in both groups will be asked to follow gynaecologists' recommendations, and are discharged once they are rehydrated and capable of maintaining adequate oral intake, which depend on the judgement of the gynaecologist.

All the three interventions will be performed in the experimental group. Before patients will be involved in the group, they will receive the psychoeducation once for 30 min, then 10 sessions of group biofeedback and TAU, for 2 weeks. If patients will be discharged within 2 weeks, they will be asked to come back to the hospital every working day to complete the rest of the treatment.

In the control group, patients will receive the psychoeducation once for 30 min before they will be allocated in the group, and then TAU only. They can be discharged once they will be rehydrated and capable of maintaining adequate oral intake. They will be asked to measure HRV once again after 2 weeks, whether discharged or hospitalised.

Primary outcomes

Literature showed that reduction of psychosomatic syndromes, as well as improvement of severity of nausea/vomiting, HRV and QoL, might represent relevant outcomes to determine the efficacy of a specific intervention focused on HG.[4 7] Moreover, the inclusion of both categorical (ie, DCPR-R syndromes) and continuous (ie, nausea/vomiting severity, HRV index and QoL) variables as primary outcomes, could greatly support the efficacy of the treatment, in the event that improvements of both kinds of variables would be detected.

Psychosomatic syndromes

A revised version of the Semi-Structured Interview based on DCPR-R[18] will be used to assess the presence of psychosomatic syndromes. DCPR-R have a modular structure including four domains (ie, stress, illness behaviour, psychological manifestation, personality), and allow the formulation of 14 diagnostic rubrics: allostatic overload,

health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatisation, alexithymia, conversion symptoms, anniversary reaction, somatic symptoms secondary to a psychiatric disorder, demoralisation, demoralisation with hopelessness, irritable mood, type A behaviour and alexithymia. The interview has 79 yes/no items and focuses on the past 12 months. The updated version of DCPR[18] was developed based on insights derived from their use in a large number of samples and settings[17] and it includes the diagnostic criteria for two additional syndromes, allostatic overload and hypochondriasis. Both allostatic overload and hypochondriasis can be assessed by specific climetric criteria[26 27] that underwent validation.[27–29] The use of DCPR was reported to be useful and reliable in the assessment and description of psychosomatic distress in general, medical and psychiatric populations, showing excellent inter-rater reliability, construct validity and predictive validity for psychosocial functioning and treatment outcome.[30–32] Skip instructions are provided and some questions do not need to be asked. Some items can be completed based on the interviewer's observation and clinical judgement without specific questioning. If participants will be discharged in less than 2 weeks, they will be reached by telephone to undergo the interview.

Severity of nausea/vomiting

The modified Pregnancy-Unique Quantification of Emesis and Nausea (modified-PUQE),[33] a 3-item self-rating scale that incorporates three dimensions (ie, nausea, vomiting, retching), will be used to assess the severity of nausea/vomiting. It represents a valid index for the assessment of nausea/vomiting severity and its use is justified to assess global nausea/vomiting severity in the first trimester of pregnancy. The respondents are asked to indicate—on a 5-point Likert scale—the extent to which they agree with each statement. The sum score may range from 3 to 15. 3–6 represents mild nausea/vomiting; 7–12, moderate nausea/vomiting and 13–15, severe nausea/vomiting. The infraclass correlation coefficient was 0.71, and the severity of nausea/vomiting that was measured by the modified-PUQE was associated with QoL.[33]

HRV index

The biofeedback system (Heartmath, VISHEE, Nanjing) is used to monitor and record the HRV index, including the SD of normal-to-normal intervals (SDNN) between adjacent heartbeats, high frequency (HF) and low frequency (LF)[34] HRV, and the ratio between LF and HF (LF/HF). SDNN represents the amount of variability in heartbeat intervals for a given time period; in this study 5 min time intervals at preintervention and postintervention are used.[35] The higher values of SDNN, the better health outcomes. HF HRV reflects parasympathetic activity and typically corresponds to the range between 0.15 and 0.40 Hz.[36 37] LF HRV is influenced by both the sympathetic and parasympathetic systems, baroreflex

activity and typically corresponds to the range between 0.05 and 0.15 Hz.

Quality of life

Short-Form Health Survey with the standard 12-item version (SF-12)[38] will be used to measure QoL. This shorter version of the commonly used SF-36 yields two summary measures of physical and mental health. Summary measures will be calculated by adding the scores of the 12 items, with a range from 0 to 100; higher scores represent better QoL. The relative validity ranged from 0.43 to 0.93 (median 0.68) for physical health, and 0.60–1.07 (median 0.84) for the mental health.[38]

Secondary outcomes

Days of hospitalisation

Length of hospitalisation after enrolment, as recorded the patients' hospitalisation days between preintervention and the discharge from the hospital. Patients are discharged once they are rehydrated and capable of maintaining adequate oral intake, on the decision of their gynaecologists. The longer length of hospital stays, the higher the economic costs are.

Rehospitalisation for HG

The repeated hospitalisation for HG after the intervention until 20-week gestation, as measured follow-up after their first discharge from the hospital. All the participants will be asked by telephone whether they have received the HG treatment again after discharge, up to 20-week gestation.

Laboratory investigations

Ketonuria, renal function, serum electrolytes and full blood count results represent measures of severity of HG during hospitalisation. All the participants will undergo the laboratory investigations at T0 and T1.

Monitoring

On the basis of the no risk of harms associated with the non-pharmaceutical intervention in this Clinical Trials of an Investigational Medicinal Product trial, no interim analysis or data monitoring committee is planned.

Confidentiality

All data will be anonymised to ensure patient confidentiality is protected. A unique research number will be used to identify the participants' data in the database. Data will be kept securely and only the investigators have access to the data.

Evaluations

The participants in both groups will be evaluated with the SSI based on DCPR-R, SCID for DSM-5, modified-PUQE, HRV index, QoL and laboratory investigations before the treatment (T0), at the end of the treatment (ie, 2 weeks later) (T1). Days of hospitalisation and number of repeated hospitalisation will be assessed as well at T2.

Participant timeline

Participants are identified at the Department of Gynecology according to eligibility criteria and exclusion criteria by research staff. Following gaining written consent, participants are immediately randomised to the control group or the intervention group. For those patients randomised to the control group, psychoeducation and TAU will be administered. For the intervention group, patients will receive 2-week biofeedback intervention additionally. The assessment of DCPR-R, modified-PUQE, HRV, QoL and laboratory investigations will be conducted before and after 2-week treatment, days of hospitalisation and rehospitalisation for HG will be collected until 20-gestation week for both groups.

Sample size

Based on a previous trial about psychotherapy on nausea and vomiting of pregnant women, the SD of modified-PUQE in nausea and vomiting pregnant women is 3.[39] To detect a medium effect size (f=0.25) at the statistical power of .90 based on a two-sided significance level .05, a minimum sample of 44 participants will be required. Given an attrition rate of 35%, as observed in other biofeedback intervention trials,[40] it is expected to recruit at least 68 patients. G*Power3.1 has been used to calculate the sample size.

Patient and public involvement

Gynaecology doctors from the Department of Gynecology of Changzhou Maternity and Child Healthcare Hospital were consulted in the development of the trial and reviewed the protocol. They provided valuable insights which led to considerations of ethical issues as well as feasibility, which resulted in the changes in inclusion criteria, outcome measures and continued treatment after the end of intervention. They introduced the project to their patients who will decide for themselves to participate in the research or not. The intervention fee of the experimental group would be paid by the two funding. We plan to inform the trial participants of the final results if requested.

Data access

Full access to the dataset will be held by the principal investigators, coinvestigators and statistician only.

Statistical analysis

All the data will be analysed with the SPSS V.22.0. Repeated measures Analysis of Variance (ANOVA) will be implemented to evaluate between and within groups changes in modified-PUQE, HRV index, QoL (primary outcome) and the laboratory investigations (secondary outcome). The reduction of the frequency of DCPR-R syndromes will be analysed by means of logistic regression. Independent sample t-test will be used to analyse differences concerning length of hospitalisation (measured in days) and number of repeated hospitalisation between two groups. Pearson χ^2 tests and independent samples t tests will be performed to assess statistical differences on clinical and sociodemographic characteristics between two groups. In addition, Pearson χ^2 tests will be used to assess the rate of moderate and severe nausea/vomiting in both groups preintervention and postintervention, respectively. Missing data will be dealt by means of multiple imputation procedures. The differences will be considered significant with a p value ≤0.05.

ETHICS AND DISSEMINATION

This study has received ethical approval from the Nanjing Medical University (No. 2019/491, granted 22 February 2019). All the data will be uploaded online to ResMan raw data sharing platform of China Clinical Trial Registry. All participants will be required to provide written informed consent (see online supplemental material 1). Study outcomes will be disseminated through peer-reviewed publications and academic conferences, and they will be used to pave the ground to a tailored biofeedback intervention for patients with HG with psychosomatic syndromes.

DISCUSSION

The DSM-5 has been regarded as the gold standard of psychiatric evaluation.[41] Anxiety and depression were common in the first trimester among HG women assessed during their first hospitalisation, with caseness rates of 20.6%~46.9% and 29.2%~47.8%, respectively,[42] 36.3% and 22.1% from a longitudinal study of Chinese women in Hong Kong.[43]

However, the methodological flaws in studies have left the concept that anxiety and depression as a cause or outcome of HG unsupported by evidence,[44] and psychiatric diagnoses are not highly represented among women with HG who feel less overall healthy during the pregnancy.[45] First, the bulk of the existing data does suggest that even if women with HG feel less generally healthy during the pregnancy, psychiatric diagnoses are not over-represented longitudinally.[45] Most of the previous studies[46] used self-reporting scales (Beck Anxiety Inventory, Beck Depression Inventory, Hospital Anxiety and Depression Scale, Edinburgh Postnatal Depression Scale, Spielberger Anxiety Index) to screen and diagnose anxiety and depression, without structured psychiatric interview and observer-rated evaluation. Second, in the psychiatric medicine literature, demoralisation during a medical illness is often misdiagnosed with depression.[45] Even though some symptoms can overlap with depression, patients with demoralisation will have significant mood improvement when their medical circumstances improve, and this characteristic seems particularly applicable to women with HG and should diagnostically be considered first and foremost.[45] Third, psychosomatic aspects of HG has been proposed since 1984,[47] but there is still no appropriate assessment tool performed in the clinical practice with these patients.

Compared with DSM-5, DCPR have been regarded as a more sensitive tool in detecting psychosomatic suffering,[48 49] and showed their clinical utility in subtyping medical patients, identifying subthreshold or undetected syndromes, evaluating the burden of somatic syndromes, predicting treatment outcomes, and identifying risk factors.[17]

It is possible that in some women, vomiting becomes a conditioned or anticipatory response and—for this reason—it would be amenable to interventions such as psychotherapeutic approaches.[50] Literature showed positive results obtained with hypnotherapy[51] in treating nausea/vomiting in HG women. However, these findings were obtained from case series and did not include control groups, which makes difficult to differentiate true treatment benefits from normal recovery. Additionally, some patients could experience contradictory arousal effects deriving from some relaxation exercises in psychotherapy, which could make them more nervous and anxious.[52 53] Therefore, in this study, group biofeedback is selected as an intervention that allows patients to monitor their own emotional state in real time, during the treatment.

Biofeedback has been used to reduce perinatal anxious and depressive symptoms, and its safety for pregnant women is beyond doubt.[23] The three working principles (ie, HRV, Jacobson's muscle relaxation and guided imagery) have been applied to improve physiological and psychological functions.[54] HRV, a key marker of parasympathetic functioning and a potent predictor of physical morbidity and mortality,[55] involves learning how to breathe at a resonance frequency rate, typically about 6 breaths/min. Autonomic nervous dysfunction is also considered to be one of the possible aetiology for HG.[9] HRV biofeedback training increases baro-reflexes and helps people develop healthier breathing patterns, and it permits the upregulation of the body ability to balance environmental change and physiological needs by improving baroreceptor and parasympathetic function.[40] Jacobson's PMR constitutes a systematic technique for achieving a deep state of relaxation through a progressive tensing and relaxation of various muscle groups. Application of PMR has been shown to reduce stress and anxiety, to improve symptoms such as tension headaches and insomnia, and to make a positive contribution to adjuvant therapy in cancer, chronic pain management in inflammatory arthritis and irritable bowel syndrome.[56] Finally, guided imagery represents a tool to encourage subjects to enter a safe, calm, content and relaxed state. A positive imagery activity is verbally introduced by the computer as a narration of thoughts and suggestions that guide the listener's imagination. Psycho-neuro-immunological theories propose that the psychological response to guided imagery may downregulate the hypothalamic–pituitary–adrenal axis, resulting in a reduced stress response, increased immune function and greater sense of well-being.[57]

Compared with the control group, participants in the experimental group are expected to experience a significant decrease in the severity of nausea and vomiting, improvement of HRV index and laboratory results, better QoL, shorter hospitalisation stays and lower frequency rehospitalisation for HG after the intervention. Findings from this study would contribute to a sensitive diagnostic criteria of psychosomatic symptoms for patients with HG, and the development of a tailored protocol of group biofeedback intervention to improve HG-related symptoms among both inpatients and outpatients with psychosomatic syndromes.

Two limitations of the study should be acknowledged. First, since this study will be a single-blind trial, patients will know whether they undergo biofeedback therapy and, therefore, the placebo effect of biofeedback in the experimental group could not be excluded. Second, given that the DCPR-R syndromes are conceived as categorical constructs, we cannot ascertain the modification of symptoms severity following biofeedback therapy, but we will evaluate relief of DCPR-R syndromes after the 2-week therapy.

Trial status

This study describes the first version of the protocol (V1.0). Patient recruitment is currently ongoing. If the protocol needs to be amended, the relevant parts of the study will be updated, and the changes will be recorded in the clinical trials registry. Due to the impact of COVID-19, our related researches have been severely affected, and will be appropriately postponed. The first patient has been enrolled on 20 August 2020, and it is expected to finish by the end of 2022.

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