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Official Title: Prospective Longitudinal Pilot Study on the Association between Treatment of Allergic Rhinitis and Cognitive Ability in Children

Date: 11 April 2018

Study Protocol and Statistical Analysis Plan

INTRODUCTION
Allergic rhinitis is the reportedly second most common reported chronic health condition in Hong Kong children under the age of 14, with the Child Health Survey 2005-2006 indicating a prevalence of 24.5% [1]. Allergic rhinitis is a type I hypersensitivity reaction, which occurs when IgE antibodies are produced against allergens, leading to the activation of mast cells which release inflammatory mediators. Common allergens in Hong Kong include house dust mite and cockroaches [2]. Allergic rhinitis causes a multitude of symptoms including itching, sneezing, nasal discharge, post-nasal drip, and nasal congestion. It can cause poor quality sleep, leading to daytime sleepiness, decreased cognitive ability, mood instability and fatigue. Allergic rhinitis leading to a reduction in quality of life in adults has been well established, leading to impediment of cognitive processes and poorer ability in attention-requiring activities (e.g. driving) [3]. These symptoms can similarly significantly impede a child's education and quality of life. It is estimated that up to 90% of allergic rhinitis patients are untreated, insufficiently treated, or inappropriately treated [4].

With regards to children and teenagers, some studies have suggested that allergic rhinitis can cause significant cognitive difficulties, with detrimental effects on children's education and examination performance[5], however others suggest there is no association[6]. A 2014 longitudinal cohort study on the treatment of allergic rhinitis in children showed an improvement in attention and divided attention after 1 year of treatment[7]. There are little studies regarding the effect of treatment of allergic rhinitis on cognitive abilities in children.

BRIEF SUMMARY OF STUDY
Pilot study on the association between allergic rhinitis and cognitive ability in children aged 11-14 within the same year group at school. Primary outcome measures include cognitive tests (Digit Span Test, Stroop Test, Chinese Auditory Verbal Learning Test, Verbal Fluency Test, and Trail Making Test), so as to assess the cognitive ability of allergic rhinitis patients before and after treatment compared to a control group. Rhinitis Symptom Utility Index (RSUI) of patients will be the secondary outcome measured through questionnaires. Positive skin prick test and endoscopy examination (taking place in Prince of Wales hospital) will be required before the diagnosis of allergic rhinitis. The data will be analyzed by the Multilevel models. Collectively, an estimate of 34 allergic rhinitis patients with 106 control samples are to be recruited in a secondary school. Written consent will be required prior to the study, and all participants have the right to withdraw from the study at anytime. Should any issues arise, subjects and their legal guardians may contact research staff Mr. Lam during office hours.

RESEARCH OBJECTIVES
1. To investigate, if any, the differences between normal and allergic rhinitis patients in terms of cognitive function
2. To investigate the impact of allergic rhinitis on different areas of cognitive function
3. To investigate the improvement of cognitive function in children after 8 weeks of standard treatment of allergic rhinitis

RESEARCH HYPOTHESIS
Children with allergic rhinitis are expected to have a heightened improvement in cognitive abilities after the treatment compared to the normal control group due to relief of their nasal symptoms.

STUDY DESIGN
This study is a prospective longitudinal pilot study to take place from 1 Dec 2017 to 31 Dec 2018. Final report will be completed 30 June 2019.

STUDY SAMPLE AND SETTING

The study is to be performed in Hong Kong, with subjects aged 11-14 studying Form 1 and 2 in secondary school being recruited. Recruitment and cognitive testing will take place at the secondary school, whilst physician follow up and skin prick tests will take place at Prince of Wales Hospital. Healthy individuals as well as patients with a history of allergic rhinitis will be recruited. Chinese will be the main language used. The total number of the Form 1 students within the school will be around 200. The estimated participation rate will be approximately 70%. As the prevalence of allergic rhinitis in Hong Kong children under the age of 14 is approximately 24.5%[1], the expected number of participants and students with allergic rhinitis are 140 and 34 respectively.

STUDY FUNDING

Study funding will be sourced from Department of Otorhinolaryngology, Head and Neck Surgery (ENT), Faculty of Medicine, The Chinese University of Hong Kong (CUHK).

ETHICAL CONSIDERATIONS

Ethical approval will be sought from The Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (CUHK-NTEC CREC). Legal guardians will be well-informed as to the nature of the study and if necessary, the medication treatment and possible side effects. Invitation letter (Appendix 1) will be sent and written consent (Appendix 2) will be obtained from willing participants in the study. Confidentiality of all personal data, including questionnaire responses, will be kept in accordance with the Hong Kong Privacy Ordinance. Names and other identifying information will be omitted from the electronic database. All computer records will be locked with a password. Subjects will be withdrawn from the study immediately if his/her legal guardian chooses to withdraw consent. Files will be locked in the cabinets and will only be assessed by authorized research staff.

PRECAUTIONS TO PROTECT SUBJECTS

As subjects are under the age of 18, the subjects and legal guardians will be fully informed of the nature, scope, and possible consequences of the study. This study presents no greater than minimal risk to children and their safety and welfare are of utmost importance. Legal guardians have the right to withdraw subjects from the program at any time. Standard treatment for allergic rhinitis will be prescribed by physician according to guidelines. If issues arise, research staff will be available for subjects to contact during office hours.

MATERIALS AND INVESTIGATIONS USED

Rhinitis Symptom Utility Index (RSUI)

The RSUI is a preference-weighted measure of common rhinitis-related symptoms presented in a 10-item questionnaire (Appendix 4). Five rhinitis-related symptoms (stuffy or blocked nose, runny nose, sneezing, itchy eyes, and itchy nose or throat) are assessed with a 4-point Likert scale in terms of their frequency and severity during the past 14-day period. Frequency of each symptom is judged as either "not at all", "1-3 days", "4-7 days", or "8-14 days". Severity of each symptom is evaluated as "not applicable", "mild", "moderate" or "severe". RSUI is the utility of the symptom state on a scale where the best state (no symptoms) has a score of 1 and the worst possible state (severe symptoms for 8 to 14 days) has a score of 0. [8]

Digit Span Test (DST)

Digit Span Tests are commonly seen in the Wechsler tests for intelligence. The current version used is a modified version by Lee and King (2010) [9], with higher ceiling and simplified administration to

prevent exhaustion. There are two parts of the test: forward span and backward span. Forward span serves to assess auditory sustained attention, whereas backward span tests for the participant's working memory. In the forward span test, participants listen to a series of number digits and repeats the sequence of numbers heard. The digit series will increase in length by 1 after each successful trial until the subject fails to repeat the series in its entirety. In the backward span test, the subject listens to a series of numbers, but repeats the numbers in reverse sequence. Alike the forward span test, the digit series will increase in length by 1 after each successful trial until the subject fails to recall the sequence in its entirety. The digit span test is a well-established test for the pediatric population, with multiple studies utilizing it as an assessment of working memory in children. [10]

Stroop Test (Chinese Translated Victoria Version)
To test selective attention, response inhibition and speed of information processing, the Victoria Stroop Test will be utilized. With the administration time of approximately 5 minutes, the Victoria Stroop Test is a shortened, psychometrically sound version of the original Stroop Colour-Word Test. Participants will be shown 3 cards in total, with his/her response time to each card being recorded. The first card will show dots of differing colours, with participants being asked to recite the colours shown. The second card contains a list of random words printed in different colours and the participant will be asked to name the colour of the words. The third and last card contains colour words printed in ink that is coloured different from the word, with the participant being asked to name the colour rather than read the word. The difference in the time required to respond to each of these colours allows the measurement of interference and hence the Stroop effect. The Stroop Colour and Word Test has previously been used to assess cognitive function in allergic rhinitis patients[11] and also depressive patients[12].

Chinese Auditory Verbal Learning Test
For assessment of verbal learning and memory domain, the Chinese Auditory Verbal Learning Test will be utilized. This test, based on the original Rey Auditory Verbal Learning Test, was developed by local researchers and psychologists, and has been used previously on Chinese adolescents[9]. Participants are presented with a list of 15 words (List A), and are asked to read this list aloud 5 times, with each time being followed by a free recall. Following this, an interference list of 15 words (List B) will be presented to the participant. Participants will be asked to read aloud and recall the interference list (List B), and then to recall the words from List A without further presentation. After a 30 minute delay, the participants will once again be asked to recall the words from List A without regard to order. The number of words recalled will be used as a measurement of memory retrieval. Afterwards, a list of words will be presented to the participantsand they will have to recognize those that originated from List A.

Verbal Fluency Test
Participants will be given a category and asked to list as many words as possible relating to the category (e.g. vegetables). The number of words spontaneously produced within 1 minute will be measured and used to assess one of the executive functions, sematic fluency. The Word Fluency Test has previously been used in multiple neuropyschological studies[13] and also as a tool for measuring executive functions in children [14].

Trail Making Test

Participants will be given two sheets and asked to draw a line to connect the circled numbers from smallest to largest numerically in Part A, and draw a line to connect first a circled number and then a circled alphabet in numerical and alphabetical way alternatively. The test will take 5 to 10 minutes and be used to assess one of the executive functions, selective attention. The Trail Making Test has previously been used in psychometric studies[21] and also as a tool for measuring executive functions in children.

Skin Prick Test
Widely-used test used to identify allergens responsible for triggering symptoms of type I hypersensitivity reactions. It is regarded as a safe method of investigating sensitization in children[15]. Different types of allergen will be exposed to the body through the skin. A wheal diameter >=3mm will be considered positive.

Screening Questionnaire
To screen out healthy individuals and individuals with allergic rhinitis, a screening questionnaire adopted from ISAAC (International Study of Asthma and Allergies in Childhood) Core Manual and supplementary questionnaires on rhinitis and rhinitis management[16] with extra questions added according to ARIA (Allergic Rhinitis and its Impact on Asthma) classification. ISAAC and ARIA have been shown to be useful in evaluating prevalence and severity of allergic rhinitis in school children[17]. Baseline Total Nasal Symptom Score (TNSS)[18] will also be evaluated in the questionnaire (Appendix 3).

Treatment Diary
Subjects are required to fill in an 8-week diary for drug compliance monitoring (Appendix 5). Everyday subjects are required to fill in the time at which they took the medication and are given the opportunity to jot down additional remarks. This is to ensure treatment compliance, and not for the interpretation of treatment outcomes.

SUBJECTS AND METHOD

Subjects
Students aged 11 to 14 currently studying Form 1 and 2 in secondary school will be recruited directly through invitation. Recruitment will include patients suffering from untreated allergic rhinitis in additional to healthy individuals to serve as a control group. Patients suffering from allergic rhinitis will be classified according to ARIA guidelines into mild/moderate/severe, and duration into intermittent/persistent. Patients suffering from rhinitis due to non-allergic origins or those associated with nasal polyposis or sinusitis will be excluded. Patients are going to complete the Rhinitis Symptom Utility Index (RSUI) questionnaire for assessing pre and post symptoms.

Control Group- Inclusion Criteria
1. Both genders of 11-14 years
2. Chinese in ethnicity
3. Subjects who have not been diagnosed with a long term medical or psychiatric problem
4. Subjects who are not currently undergoing any long term medical treatment.

Patient Group- Inclusion Criteria
1. Both genders of 11-14 years, diagnosed with allergic rhinitis on basis of screening instruments, medical history, clinical assessment (by general ORL examination including nasal endoscopy)
2. Chinese in ethnicity
3. Positive skin prick test with wheal diameter >= 3mm

4. Ability to understand the nature, scope, and possible consequences of the study
5. Capability and willingness to comply with the requirements of the protocol

Patient Group- Exclusion Criteria
1. Subjects with co-existing nasal conditions other than AR, which may affect nasal pathology (nasal polyposis, sinusitis, severe deviations of nasal septum, tumors of the nasal cavity, acute/chronic rhinosinusitis or any underlying pathology that might affect nasal breathing or nocturnal sleep)
2. Subjects with prior nasal surgery (e.g. nasal cavity, sinuses)
3. Subjects with known brain disorders, prior brain surgery or history of stroke
4. Subjects diagnosed with learning disability, autism or attention deficit hyperactivity disorder (ADHD)
5. Subjects with history of known sleep disorder, central or obstructive sleep apnea, narcolepsy, insomnia, patients requiring regular sleep medication and those hypersensitive to applied topical nasal steroids
6. Subjects who have taken topical nasal steroids, oral anti-histamines or medications affecting nasal symptoms 30 days prior to commencement of study
7. Subjects with hypersensitivity reactions towards topical nasal steroids or oral anti-histamines
8. Subjects previously diagnosed with any psychiatric disorders
9. Subjects who suffered from a respiratory tract infection within the past 30 days
10. Subjects who have clinically major cardiovascular, respiratory, hepatic, neurological, endocrine, immunological or other major systemic disease(s)
11. Subjects who are undergoing a long-term medical treatment plan

TREATMENT AND COMPLIANCE
Medication (complying with standard treatment guidelines) will be prescribed to the patient group. As this study does not investigate the efficacy of a specific drug, the medication plan will be up to the discretion of the attending physician with the aim of alleviating nasal symptoms. Commonly, pediatric allergic rhinitis treatment involves topical nasal steroids and 2nd generation antihistamines. Compliance will be monitored via the treatment diary, phone call after four weeks of treatment, and pill counting. Should issues arise anytime during the study, research staff will be available for subjects to contact during office hours. To increase the incentives of the participants, reinforcement programs, such as hospital visits and a health-related seminar, will be held. Each participant will receive a certificate upon completion.

METHOD OF ANALYSIS
Multilevel models, the mixed effects models [19], will be used to compare the longitudinal rate of change on cognitive function and different areas of cognitive function (as measured by Digit Span Test, Stroop Test, Chinese Auditory Verbal Learning Test, Verbal Fluency Test, and Trail Making Test) both within and between normal and allergic rhinitis patients. Multilevel models are random effects models that take into account the hierarchical nature of the data, and the within- and between-subject heterogeneity [20]. For longitudinal data, such models allow for measurements made at unequal intervals and with a varied number of measurements (i.e. subjects who may have one or several measurements). The models are fitted by the method of restricted iterative generalized least-squares algorithm of MLn for Windows software package, Version 2.0 (Institute of Education, University of London, London, UK). The likelihood ratio test is used to assess the statistical significance of the estimates at the 5% level. The model assumptions are checked by inspection of the standardized residuals for normality and constant variance.

PROPOSED TIMELINE

Week 0
A. Consent will be sought from potential subjects
B. Screening questionnaires (based on the ARIA and ISAAC questionnaires) will be given to the parents of the subjects as a preliminary assessment of the subject's condition
C. Pre-treatment RSUI questionnaire will be given and explained to those suspected to suffer from allergic rhinitis.

Week 1
A. Subjects who are suspected to suffer from allergic rhinitis will undergo a skin prick test to exclude the possibility of non-allergic rhinitis.
B. Subjects who are suspected to suffer from allergic rhinitis will then be assessed by ENT specialist to perform screening of individual's eligibility for participation in the study on the basis of medical history, clinical assessment including general ORL exam and nasal endoscopy to exclude any physical obstructions in the nasal cavities that might affect nasal breathing or nocturnal sleep.
C. Inclusion and exclusion criteria will be checked
D. Patients diagnosed to suffer from allergic rhinitis will be prescribed a personalized medical treatment which is to begin when instructed 1 week later.

Week 2
A. Subjects undergo cognitive testing (Digit Span Test, Stroop Test, Chinese Auditory Verbal Learning Test, Verbal Fluency Test, and Trail Making Test)
B. Subjects are instructed to begin personalized medical treatment the day after cognitive testing.
C. Patients are reminded not to use over-the-counter drugs or prescription medications that could affect rhinitis symptoms during the treatment period and to record any medications they take.

Week 6
Reminder calls to continue treatment plan and treatment diary to ensure compliance

Week 10
A. End of treatment plan.
B. All unused drugs will be collected to check for compliance
C. Subjects undergo cognitive testing (Digit Span Test, Stroop Test, Chinese Auditory Verbal Learning Test, Verbal Fluency Test, and Trail Making Test)
D. Subjects complete post-treatment RSUI questionnaire
E. Subjects presented with completion certificate

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