Registering the immune response to an influenza vaccination challenge in PTEN Hamartoma Tumour Syndrome

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Primary Objective: The primary objective is to analyse the humoral and cellular immune response to influenza vaccination in PHTS individuals.• Is the immune response to seasonal influenza vaccinations impaired in PHTS?• Do characteristics in humoral…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON49354

Source
ToetsingOnline

Brief title
Immune response to flu vaccination in PHTS

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Immunodeficiency syndromes

Synonym
Cowden Syndrome, PHTS

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cowden, Flu vaccination, Immune response, PHTS

Outcome measures

Primary outcome

The main study parameter will be the concentration of antibody titres established by Hemaglutination Inhibition Assays At baseline and 15 days after vaccination with the seasonal flu vaccine.

Secondary outcome

Secondary parameters will be counts per minute (cpm) as measure of T cell proliferation at baseline and at day 15. Also, the concentration of cytokines will be determined from blood samples at baseline and day 15(IFN-*, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNFα, TNF-β).

Other secondary outcomes will be the proportions of seroconversion in both groups; defined as >=4 fold increase of titer, resulting in a titer of 1:40, and the seroprotection in both groups (rise to>= 1:40). This will be tested by Chi2 test.

Study description

Background summary

PTEN hamartoma tumour syndrome(PHTS) is a hereditary tumour syndrome caused by a heterozygous mutation in the PTEN gene. It is a rare disease affecting 1 in 200000 individuals, it is theorised to be more prevalent than that , however. Many features of PHTS also exist in the general population, making detection complicated. Patients with PHTS are at high risk of developing cancer, especially breast, thyroid, endometrial and colon cancer. In recent

years, PHTS has been reported in multiple case reports and case series to feature immune dysregulation. Hypogammaglobulinemia and decreased response to Haemophilus influenzae vaccine has been reported. In one case report, an increase in transitional B cells in peripheral blood was reported in a patient with hypogammaglobulinemia. One small case series could not replicate this finding, but did note that in PHTS, immunoglobulin levels were in the lower normal range.
Recently, it has been suggested that immune dysregulation in PHTS should be considered as a contributor to increased cancer risk in this syndrome. Immune dysregulation has not yet been thoroughly studied in PHTS individuals, as the impact of losing PTEN expression has primarily been investigated in murine lineage specific PTEN knockout models. In regards to the humoral immune system, class switch recombination has been shown in B cell specific PTEN -/- mouse models, with lowered IgG and IgA, but increased IgM. Translation of these findings to PHTS individuals is difficult and investigating immune dysregulation in patients circumvents this hindrance.
Identifying the link between immune dysregulation and increased cancer risk in PHTS requires further elucidation of immune impairments in PHTS individuals. One of such impairments that is measurable and therefore objectifiable, is the humoral and cellular immune response to vaccination. The proven safety of the seasonal flu vaccination and the widespread availability of the vaccine, make it a logical and practical choice to use for this investigation. The profile in antibody response or T cell activation and proliferation after vaccination could expose immune deficiency.
Elucidation of immune impairments in PHTS may eventually lead to the finding of interesting molecular or immunological *signatures* of PHTS. These PHTS associated phenotypes could be instrumental in the detection of new PHTS diagnoses, allowing proper cancer surveillance in individuals that would otherwise be at risk and overlooked.
As PHTS is a rare syndrome, it is a challenge to include enough individuals for a study in PHTS individuals. At the moment, the Radboudumc has more than 60 PHTS patients of 18 years and older and is a centre for expertise on the subject, providing the unique opportunity to investigate this patient group and reveal the problems and the opportunities that the PHTS immune system harbours.

Study objective

Primary Objective: The primary objective is to analyse the humoral and cellular immune response to influenza vaccination in PHTS individuals.
• Is the immune response to seasonal influenza vaccinations impaired in PHTS?
• Do characteristics in humoral and cellular immune response to vaccinations point to specific dysregulation in the immune system?

Study design

The design used will be a prospective, non-randomised clinical trial with comparison group. There will be two groups that will both receive intervention at the start of study. The study will take place over a period of two months, half October through half December. This coincides with the start of the national flu vaccination campaign and includes time required for follow up. The setting of the study is in an academic medical center, Radboudumc. The Radboudumc has a large group of PHTS patients.

The study will consist of two groups of 15 individuals, one PHTS group and one group of unaffected individuals, it is the aim of the study to recruit unaffected individuals out of the partners of patients. It is our expectation that this will make the two groups more similar in terms of age, socio-economic status and environment.

At T=0, influenza vaccination will be administered, samples will be drawn for baseline T cell proliferation assay and baseline measurement of cytokines. A baseline hemagglutination assay will be performed.
At T=14 hemagglutination assay will be repeated, as well as the proliferation assay and cytokine measurements.

Influenza vaccinations will be administered at the outpatient clinic of the Radboudumc by a research nurse, after which blood sample collection will be performed by blood testing employees working at the polyclinic blood sample collection unit. After the blood samples for that day have been collected, they will be taken by the researcher to the tumour Immunology lab for analysis. At day 15, blood samples will be collected at the blood collection unit, and will be transported to the tumour immunology lab by the researcher. Test results will be reported blindly for the code the subject received. Subsequently, data will be entered into Castor fully anonymized . The key file containing subject identity and subject identification number will be guarded by a password only known to the researcher. Data will be analysed using SPSS.

Intervention

All subjects will be administered a registered flu vaccination (Influvac Tetra) at T=0.

Study burden and risks

The use of a seasonal flu vaccine as intervention medication is safe and effective. All medication has some adverse side effects, but flu vaccination is very safe and adverse effects are extremely rare. Flu vaccination programmes have been used for some time by the Dutch government for protecting vulnerable populations to influenza infection. Exposing this population to the risks of the seasonal flu vaccine will be likely to incur less damage than protection against influenza infection. It is our belief that this makes the study

ethically sound and sensible with only minor physical burden to future subjects.

This study will provide insight into immune dysregulation in PHTS using a reliable and tested method that confers little risk. By garnering new data on the dysfunction of the immune system, new venues for treatment and recognition of PHTS may emerge. Additionally, increasing knowledge on the immune system in PHTS will improve recognition and awareness of immunological symptoms in known PHTS individuals.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Diagnosed with a pathogenic PTEN mutatution leading to PHTS (for PHTS group)
-18 years or older

-Mentally capable
-Must provide written informed consent
-is registered at the radboudumc

Exclusion criteria

-Known history of relevant medical disorder, which in the investigator's judgment might have an impact on the findings of the study, or ppose additional risk to the subject by participation in the study.
-Hypersensitivity to previous influenza vaccinations
-Must not be allergic to chicken eggwhite
-Immunocomprimised patients and those receiving concomitant immunosuppressive therapy.
-Bleeding disorders such as haemophilia and thrombocytopenia.
-Must not have received vaccinations with attenuated pathogens in the 4 weeks leading up to the vaccination.
-Acute infection or recent ilness similar to to influenza.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2021
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	25-03-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL66559.091.19

Study results

Date completed:	02-03-2023
Actual enrolment:	33