Capillary malformations, from genotype to phenotype: a focus on endothelial function

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin and subcutaneous tissue disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON49348

Source
ToetsingOnline

Brief title
ACME (Amsterdam Capillary Malformation Evaluation) study

Condition

- Skin and subcutaneous tissue disorders congenital
- Skin vascular abnormalities

Synonym
Capillary malformation, port wine stain

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Afdeling biochemie en dermatologie (voor

biopsie materiaal)

Intervention

Keyword: Capillary malformation, Endothelial function, Genetic mutation, Port wine stain

Outcome measures

Primary outcome

The main study parameter is the presence of the GNAQ, GNA11, RASA1 or PIK3CA

gene mutation in study participants.

Secondary outcome

The secondary parameter is the biochemical profile, barrier function,

angiogenic sprouting capacity and wound healing properties of endothelial cells

from blood vessels of port wine stains.

Study description

Background summary

Capillary malformations, also known as port wine stains (PWSs), are vascular lesions affecting the dermis and are present at birth. They are characterized by hyperdilated capillaries and post-capillary venules. These congenital lesions occur in 0.04-2.1% of newborns and frequently appear as flat, pink macules that slowly evolve into more hypertrophic, red-to purple lesions. About two-thirds of the patients develop nodular or papular-like elements as a result of soft tissue overgrowth, leading to asymmetry, dysmorphosis, and possibly sporadic spontaneous bleeding. The stigma of a disfiguring capillary malformation can cause significant psychological burden and a decreased quality of life, especially when located in the face. PWSs can be part of a syndrome, such as the Sturge Weber syndrome and Klippel Trenaunay syndrome. Affected patients show solitary PWSs, or PWSs together with various symptoms, ranging from bone and soft tissue overgrowth to glaucoma and epilepsy due to leptomeningeal angiomatosis.

Up till now, the exact pathogenesis of PWSs is still unclear. Though, they have been linked to somatic mosaic mutations in specific G-proteins and the P110 alpha protein. Recurrent somatic variants have been uncovered in the Guanine

nucleotide-binding protein G(q) subunit alpha (GNAQ) gene, the Guanine nucleotide-binding protein subunit alpha-11 (GNA11) gene and the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene of patients with PWSs. These proteins can be found in endothelial cells and due to the abovementioned mutations, the proteins do not function properly. The genetic changes lead directly to altered endothelial cell proliferation, differentiation, and survival. Uncontrolled angiogenesis because of increased endothelial cell proliferation results in PWSs, with tangling of the capillaries in the dermis of the skin and in the brain.

When looking at a cellular level, PWSs seem to demonstrate hyperactive and hyperproliferative endothelial cells, enlarged vessel lumens and disorganized perivascular cells. But, it is still unclear how the genetic mutation relates to differences in endothelial function and characteristics of the PWS, such as hypertrophy.

Currently, no cure has been found yet for PWSs and treatment outcomes are still far from optimal.Treatment is hence mostly focused on refraining symptoms. Also, there is a large variation in treatment response that is difficult for physicians to predict. Theoretically, this variation in response could be the due to abovementioned genetic mosaic mutations. Over the last years, there has been an increased interest in the complex interactions between the genetic alterations and the phenotypic characteristics of PWSs. Unravelling the role of the genetic mutations will not only lead to new insights on the origin of PWSs, but may possibly also lead to a better understanding on why certain PWSs do not respond properly to modern therapies. In this way, new therapeutic strategies could be designed, mostly based on molecular analysis. Identifying the effector pathways of the genes that underlie PWS formation will allow for the development of more specific targeted therapies to approach their treatment. It may be a new path towards personalized medicine.

Study objective

We aim to provide preliminary information on the presence of GNAQ, GNA11, RASA1 or PIK3CA gene mutations, assess the endothelial cell properties and compare it to the phenotypic characteristics of the PWSs of affected patients. This will lead to a more comprehensive framework by which PWSs can be classified and managed.

Study design

The study design will be a prospective case series. It will be a mono-center study, carried out at the department of dermatology at the Amsterdam UMC location AMC. The study is expected to take 6-12 months as we intend to include 20 participants.
Approximately 8 patients with port wine stains visit the outpatient clinic per

week at the department of Dermatology in the Amsterdam UMC.

Study burden and risks

The study subjects will undergo two skin biopsies during their regular laser treatment. These skin biopsies are <4 mm, therefore the skin is likely to cure on its own. If the skin biopsy wound keeps bleeding after applying firm pressure during 10 minutes, the wound will be closed with Dermabond skin glue or one non-resorbable suture. There are relatively small risks with participation: a small risk on prolonged bleeding of the wound and a small risk on skin infection.

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

Adult patients with capillary malformations currently undergoing lasertherapy at the Amsterdam UMC location AMC.

Exclusion criteria

Children and incapacitated patienten.
Patients with a mix of different vascular malformations.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-04-2021
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	16-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL75128.018.20