Cytokines, autoantibodies and astrocytes in the pathology of Aicardi-Goutieres syndrome (AGS)

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Ethical review	Approved WMO
Status	Pending
Health condition type	White blood cell disorders
Study type	Observational non invasive

Summary

ID

NL-OMON34842

Source
ToetsingOnline

Brief title
NIMBL = Nuclease Immune Mediated Brain and Lupus-like conditions

Condition

- White blood cell disorders
- Cytoplasmic disorders congenital
- Central nervous system infections and inflammations

Synonym
congenital brain inflammation, congenital encephalopathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum

Source(s) of monetary or material Support: EU

Intervention

Keyword: autoimmune disease, congenital encephalopathy, microcephaly, systemic lupus erythematosus

Outcome measures

Primary outcome

We have previously shown that this test helps to discriminate AGS from viral

disease. This current study will expand these data by screening blood and CSF

from AGS patients and controls for a more extensive set of cytokines,

chemokines and growth factors using available Luminex technology.

Primary outcome measures:

- new sensitive diagnostics for AGS in blood and/or CSF

- determine the sensitivity of these parameters over time (since the

inflammatory features in AGS ultimately wane ["burning out"])

- serum autoantibodies against standard autoantigens and tissue materials

(routine diagnostics, including brain)

- assess the time course of cytokines and presence or appearance of

autoantibodies in relation to clinical disease

Secondary outcome

n.a.

Study description

Background summary

Aicardi-Goutières syndrome (AGS) is a genetically determined encephalopathy whose importance from a clinical viewpoint is magnified because of the risk of misdiagnosis as the sequelae of congenital infection. Moreover, from a biological perspective it is remarkable that some children with AGS develop an early-onset form of systemic lupus erythematosus (SLE).

AGS and congenital infection are associated with an increased production of interferon alpha (IFN-*), and a disturbance of IFN-* homeostasis is considered central to the pathogenesis of SLE. These observations led us to predict that elucidation of the pathogenesis of AGS would inform our understanding of autoimmunity.

We have shown that AGS results from mutations in genes encoding the exonuclease TREX1 (AGS1) and subunits of the RNASEH2 endonuclease protein complex (AGS2, AGS3 and AGS4), and, the recently identified AGS5 gene and its protein. Although AGS is normally inherited as a recessive trait, we have described heterozygous TREX1 mutations in dominantly inherited AGS, in a cutaneous form of SLE called familial chilblain lupus (FCL), and in patients with an adult-onset cerebro-retinal microangiopathy associated with Raynaud*s phenomenon (retinal vasculopathy with cerebral leukodystrophy: RVCL). Considering the phenotypic and biochemical overlap of AGS with lupus, it is notable that heterozygous TREX1 mutations were also present in 2% of a cohort of individuals with SLE. We group AGS, FCL, RVCL and (some cases of) lupus as Nuclease Immune Mediated Brain and Lupus-like (NIMBL) phenotypes.

This project will focus on AGS (and RVCL) as paradigm for other disorders sharing the common pathogenesis.

Study objective

The objectives of the complete NIMBL study are as follows:

Objective 1. Gain insight into the natural history of AGS and RVCL
* Create a registry of paediatric and adult AGS and RVCL patients, and develop a network of clinicians caring for these patients
* Comprehensively define the clinical, radiological and laboratory features of AGS and RVCL
* Evaluate disease features which may pertain to heterozygous carriers of TREX1, RNASEH2A/B/C and AGS5 mutations in AGS families

Objective 2. Acquire knowledge for the development of diagnostic and therapeutic modalities
* Diagnostics
* Define the molecular spectrum of mutations in TREX1, RNASEH2A/B/C and AGS5 in AGS and RVCL and correlate this with disease phenotype
* Establish a protocol and quality assurance for the molecular diagnosis of NIMBL phenotypes

* Produce validated diagnostic criteria
* Identify non-TREX1 / RNASEH2A/B/C / AGS5 mutation-associated AGS patients and define novel genes causing this disease
* Therapeutics
* Collect data on the efficacy of immunomodulators in AGS
* Collect data on the effectiveness of current treatments for specific features (e.g. chilblains / Raynaud*s / thrombocytopenia / seizures / headaches) of AGS and RVCL
* Identify disease features and biomarkers for monitoring future therapeutic trials
* Use our new model systems to test therapeutic strategies identified by the NIMBL project

Objective 3. Develop four new animal models relevant to human NIMBL phenotypes
* Ags5 conditional knock-out mouse
* Rnaseh2c knock-in mouse
* Trex1 conditional knock-out mouse
* RVCL Trex1 knock-in mouse

Objective 4. Explain the pathophysiology of NIMBL phenotypes
* Dissect out the intracellular mechanism signalling retained nucleic acids to immune activation
* Characterise the source, abundance, diversity, size, and dynamics of Trex1 DNA substrates
* Define key aspects of the cell biology of TREX1 and the AGS5 protein
* Determine if / how the pathogenesis of AGS and RVCL differ
* Interrogate cytokine, autoantibody and astrocyte function in AGS

Study design

Our local study effort is to measure cytokines and other biomarkers in paired CSF and serum samples for AGS-related neuroinflammatory reactions (*cytokine storm*).
In view of the apparent *burning out* of the disease process with time, it will be of particular importance to measure outputs in early and later stages of the disease.

Serum samples of AGS patients will be screened for autoantibodies against a panel of usual autoantigens as well as donor tissues (including skin, heart, liver) for potentially AGS-specific autoantibodies.

We will characterise the time-course of these parameters (cytokines and autoantibodies) to determine associations with phenotypic features (including age at onset and rate of disease progression), and with genotype.
Significant results will then be interrogated further by: 1) examining production and release of these factors upon cellular activation of fibroblast and PBMC cultures derived from AGS patients and controls; 2)

immunohistochemistry of AGS brain sections with relevant antibodies and appropriate cell-specific counterstaining to characterise the cellular origin of the marker of interest , and 3) staining of patient chilblain lesions upon any diagnostic skin biopsies for the selected cytokines and for cell-specific markers including plasmacytoid dendritic cells and T cells.

Materials to be studied will consist of:
- Blood and CSF upon diagnostic sampling
- Monitoring blood samples (every 3-12 months) and score disease-related features of AGS
- Monitoring CSF samples upon follow-up during clincial disease progression and MRI (under anesthetics)
- Fibroblast cultures from diagnostic skin biopsies (outpatient care unit)
- Skin biopsies when available for diagnostics in case of chilblains or other disease-related tissue sampling
- Autopsy material when consented to by parents or caregivers

Study burden and risks

The burden and risks for the patient will not be increased by participation to the study.

Local care upon admission for diagnostics and/or monitoring of AGS at the early stage of the disease will be provided by colleague pediatric neurologists and pediatricians at the local academic and non-academic hospitals in The Netherlands.

Once the diagnosis is made, we will ask for consent to visit our clinical center once every 3-12 months, depending on the contact with local phycisians, the clinical condition of the patients and the consent of the parents or caregivers of the affected patients to travel to Amsterdam.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

AGS as diagnosed by pediatric neurologist

Exclusion criteria

no similarity to AGS

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending

Start date (anticipated):	01-03-2010
Enrollment:	10
Type:	Anticipated

Ethics review

Approved WMO 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	NL31715.018.10