B7 Coreceptor Molecules as Clinically-Relevant Surrogate Biomarkers in the Hyper IgD Syndrome (HIDS) form of Mevalonate Kinase Deficiency (MKD)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37741

Source
ToetsingOnline

Brief title
B7 coreceptor molecules as biomarkers in HIDS

Condition

- Other condition
- Immune system disorders congenital
- Immune disorders NEC

Synonym
hyper-IgD syndrome, mevalonate kinase deficiency

Health condition

erfelijke autoinflammatoire ziekte

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: ZonMW (VIDI subsidie),Grant van National Institute of Health (NIH);Bethesda;Verenigde Staten

Intervention

Keyword: Autoinflammatory syndrome, B7 coreceptor molecules, Hyper-IgD syndrome, Mevalonate kinase deficiency

Outcome measures

Primary outcome

Key data elements (outcome measures) are summarized in Table I (page 14) of the

protocol. These will be quantified at each of 4 collection time points.

Secondary outcome

Not applicable

Study description

Background summary

Cholesterol and isoprenoids are critical in membrane biogenesis, embryonic development, intracellular signal transduction, vesicular trafficking, and cell cycle progression (Goldstein et al 2006; Gong et al 2006a,b).
HIDS/MKD is an autoinflammatory disease characterized by systemic inflammation without an apparent infectious etiology. Mevalonate kinase deficiency (MKD) is a human enzyme deficiency with diverse phenotypes, including severe mevalonic aciduria (MA) and HIDS (Drenth, 1999; Simon, 2004). Clinically, MA and HIDS are distinguished based upon the extent of neurologic involvement, which is prominent in MA and predominantly absent in HIDS (Prietsch, 2003; Hoffmann, 1993). Both individuals with MA and HIDS may present with hepatosplenomegaly, lymphadenopathy, anemia, increased erythrocyte sedimentation rates and levels of C-reactive protein, leukocytosis, and increased urinary leukotriene excretion (Prietsch, 2003). People with HIDS suffer recurrent febrile crises during childhood characterized by elevated serum IgD and IgA1 levels, skin

rash, arthralgia and myalgia (Rigante, 2009; Steichen, 2009; Touitou, 2008; van der Hilst, 2008; Sornsakrin, 2008), yet studies by Ammouri and coworkers (Ammouri, 2007) suggest a poor correlation between elevated IgD in serum and MKD. With regard to pathogenic MVK (the gene responsible for the phenotypic spectrum of MKD) mutations, the c.1129G>A (p.V377I) is pathognomonic for the HIDS form of MKD, and this allele confers temperature sensitivity to the MVK protein (Houten, 2002).

MVK and inflammation: Patients with MKD exhibit dysregulation of IL-1*, a major inflammatory cytokine. Stimulated peripheral blood mononuclear cells (PBMCs) cultured from individuals with MKD hypersecrete IL-1*, and this is exacerbated by addition of lovastatin (Drenth, 1996; Frenkel, 2002). Hypersecretion of IL-1* was recently shown to be linked to a shortage of geranylgeranylated proteins (Houten, 2003a and 2003b; Mandey, 2006b). More recently, Marcuzzi and coworkers (Marcuzzi, 2008) recapitulated the inflammation observed in MKD by administering aminobisphosphonates (which inhibit the mevalonate pathway) to BALB/c mice. Intervention with exogenous isoprenoids (geraniol, farnesol and geranylgeraniol) effectively reversed the aminobisphosphonate-induced inflammation. We speculate that a deficiency in dolichol production, linked to loss of MVK activity since dolichol is made from isoprenoid precursors, could lead to aberrant protein glycosylation and shedding or secretion of IgD which is normally present as membrane-bound immunoglobulin in B lymphocytes. We further hypothesize that shortage of dolichol results in aberrant expression of costimulatory B7-glycoprotein expression on various cell types (see below). Finally, if oxysterol production is altered in MKD, this could alter immune function (Hannedouche, 2011).
Costimulatory B7-glycoproteins in the MKD mouse model of HIDS: We determined the activation status and proliferative capacities of splenic lymphocyte populations from Mvk+/- mice, a phenocopy of HIDS. Mvk-/- mice are embryonic lethal, while Mvk+/- mice demonstrate increased serum levels of IgD, IgA1, and TNF*, temperature dysregulation, hematological abnormalities, and splenomegaly. Flow cytometry analysis of cell surface activation markers on T and B lymphocytes, and macrophage populations, demonstrated aberrant expression of B7 glycoproteins in all splenic cell types studied. In Mvk+/- CD4 and CD8 T cells, alterations in expression of CD25, CD80, CD152, and CD28 were observed (Fig. 2, upper left and right quadrants). Mvk+/- splenic macrophages expressed altered levels of CD80, CD86, CD40, and CD11c (Fig. 2, lower left quadrant), while Mvk+/- B lymphocytes had differential expression of CD40, CD80, and CD86 (Fig. 2, lower right quadrant).
We postulate that imbalances in the expression of cell surface proteins necessary for activation, proliferation, and regulation of the intensity and duration of an immune response may result in defective T cell activation, proliferation, and effector functions in the murine HIDS model, and potentially in human HIDS. We will examine this hypothesis in HIDS patients, and will further determine if these B7 glycoprotein molecules correlate with clinical severity, other known biomarkers of HIDS, as well as isoprenoid metabolites reflecting overall cholesterol pathway function. Our studies hold promise for

identifying surrogate biomarkers specific for human HIDS, and will simultaneously expand our limited understanding of the pathophysiology of this rare disorder.

For figures and references: see study protocol.

Study objective

The objective of this study is to assess potentially new and unique biomarkers that will be specific to patients with HIDS as surrogate outcomes for eventual larger, cohort-controlled clinical studies. Our longitudinal design in a small pilot group will also identify new mechanisms of pathophysiology in HIDS patients. The primary hypothesis is that the costimulatory B7 glycoprotein abnormalities identified in the murine MKD model will be recapitulated in sera obtained from human HIDS patients, either before, during, or after febrile episodes. The secondary hypothesis posits that B7 glycoprotein molecule levels will correlate with clinical symptomatic severity score, other known biomarkers of HIDS (IgD, IgA and IL-6), markers of inflammation (CRP/ESR and leukocyte count), and/or markers of isoprenoid metabolism (lathosterol as a measure of cholesterol synthesis, cholesterol and oxysterols, urine mevalonic acid (MVA), farnesyl glucuronide, dolichol and ubiquinone, among others).

Study design

Observational prospective pilot study.

To begin, at least 14 days following any fever or symptoms from the last febrile episode, research participants will begin a 24 hour urine collection and obtain a blood draw at the end of this 24 hour period. Body temperature and clinical symptom monitoring will begin at this time. Once a temperature of *100.4*F (*38.0*C) as well as a combined clinical score of * 20 is noted, participants will be considered to be in a febrile episode. At this time, a second 24-hour urine collection period will begin, followed by a second blood draw at the end this second 24-hr urine collection period. After 72 hours from the beginning of the febrile episode, participants will begijn a third 24-hour urine collection, followed by a third blood draw. As soon as the participants body temperature returns to <100.4*F (<38.0*C) as well as a combined clinical score <20, participants will begin a final 24 hour urine collection period, followed by a final blood draw. A follow-up visit or phone call will be conducted one month after the final specimen collection to record any adverse events.
During the entire study, participants are instructed to follow their usual diet. As far as medications, use of abortive or symptomatic medications, including anakinra or steroids, as well as medications used on demand (e.g. antipyretics/analgesics) will be prohibited for this single febrile episode.

The study design is summarized in Fig. 3, page 13, of the protocol.

Study burden and risks

- Venipuncture: The vein in which the needle has been inserted to draw blood may become sore and red. A temporary *black and blue mark* may develop, and rarely fainting may occur. Blood draws will cause some minor pain and carry a small risk of bleeding and/or infection at the puncture site. A blood clot could develop and go to the lungs. Such problems are exceedingly rare.
- Skin Biopsy: The risk of a skin biopsy includes scarring, bleeding, or infection.
- Being off medication: Risk includes increased temperature, and exacerbation of usual HIDS symptoms during a febrile episode. This is a burden to the patient because of fever, pain and general malaise. Without treatment, a HIDS attack will end spontaneously in about 5-6 days.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

Male and female individuals, 18 years of age and older, with an established diagnosis of HIDS (by molecular genetic analysis).

Exclusion criteria

1) the patients* inability to donate blood or urine; 2) current history of cancer, renal failure, diabetes, liver disease, thyroid diseases, major infectious diseases, or immunodeficiency; 3) pregnancy; and 4) inability to give consent.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-04-2013
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO

Date:	20-09-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	03-03-2015
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	NL40490.091.12