Immune paralysis in trauma patients: an explorative study

Published: 07-12-2011
Last updated: 30-04-2024

Identifying the factors and underlying mechanisms involved in the pathogenesis of immune paralysis in trauma patients. Mapping the time-course of immune paralysis in trauma patients.

Ethical review	Approved WMO
Status	Pending
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON35513

Source
ToetsingOnline

Brief title
Immune paralysis in trauma patients

Condition

- Immune disorders NEC

Synonym
Immune paralysis, impaired function of the immune system following trauma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Immune paralysis, Immunity, Trauma

Outcome measures

Primary outcome

Cytokine production following ex vivo whole blood stimulation to identify immune paralysis.

Secondary outcome

Plasma mtDNA concentrations, mRNA expression levels of genes known to be involved in immune paralysis, other DAMP concentrations in plasma, infections, blood gas values, vital parameters, age, body mass index, trauma mechanism, Injury Severity Score (ISS), use of medication, surgical interventions.

Study description

Background summary

Despite numerous efforts to improve trauma care and traffic safety, trauma still remains one of the major causes of death in people under the age of 50 in the Western world. Patients die either shortly after trauma due to sustained injuries, or after several days/weeks, often due to post-injury immunological complications caused by a dysfunctional immune system, called immune paralysis, such as sepsis and multi organ failure (MOF).Immune paralysis is a condition frequently observed after trauma. This condition is characterized by unresponsiveness of the immune system to pathogens. It has been suggested that immune paralysis is caused by a pronounced compensatory reaction to activation of the immune system shortly after trauma. Another hypothesis involves the exhaustion of the immune system by the initial hit.
A number of clinical trials with immunomodulatory interventions have been performed in an attempt to prevent immune paralysis in trauma patients. However, no definite conclusions can be drawn from these studies. In order to identify targets for preventive and/or therapeutic treatments, additional knowledge on the factors involved in pathogenesis of immune paralysis is necessary. Moreover, it is crucial to map the time-course of the immune response to the initial trauma and state of the innate immune system after

trauma, to identify immunoparalyzed patients eligible for tailor-made immunomodulatory treatment.
The immune system is activated by binding of pathogen associated molecular patterns (PAMPs) to pattern recognition receptors (PRRs). As such, pathogens can be recognized via this route, but PRRs also bind so-called danger associated molecular patterns (DAMPs). DAMPs are factors that are released by damaged or stressed cells. In case of trauma, extensive tissue damage leads to the release of large amounts of DAMPs. Therefore, it appears plausible that DAMPs have a major impact on the immune response following trauma.
Recently it was discovered that mitochondrial DNA (mtDNA) represents a DAMP in trauma patients. Increased concentrations of mtDNA have been reported in trauma patients. The similarities between mtDNA and bacterial DNA result in the binding of mtDNA to PRRs recognizing bacterial DNA. Zhang et al recently described inflammatory responses following injury caused by circulating mitochondrial DAMPs. These inflammatory responses could ultimately lead to the development of immuno paralysis.
In this study, we will investigate the levels and effects of DAMPs, with an initial focus on mtDNA, in trauma patients. A relation between the presence of mtDNA and the development of immune paralysis could indicate a role for mtDNA in the pathogenesis of immune paralysis and therefore be a potential therapeutic target.
Next to the investigation of DAMPs/mtDNA, this study also focuses on mechanistic factors involved in immune paralysis. It has been suggested that decreased Human Leukocyte Antigen - DR (HLA-DR) expression on monocytes plays a role in, or is indicative for the development of immune paralysis. Suppression of Tumorigenicity 2 (ST-2) is a negative regulator of macrophage function and is also described to be important in immune paralysis. IL-1R-associated kinase-M (IRAK-M) is an inhibitor of the innate immune response has been linked to immune paralysis in septic patients. Analysis of mRNA expression of these factors and its time-course could provide more insight on the relation between immune paralysis and the expression of HLA-DR, IRAK-M, ST-2 and other potential markers.
In conclusion, the aim of this observational study is to determine the relation between factors released after trauma, e.g. mtDNA, and the development of immune paralysis, the time-course of the inflammatory response to injury and state of the immune system following trauma, and the underlying cellular mechanisms of immuno paralysis. This could result in the identification of predictive markers, potential therapeutic targets and a timeframe for therapeutic intervention.

Study objective

Identifying the factors and underlying mechanisms involved in the pathogenesis of immune paralysis in trauma patients. Mapping the time-course of immune paralysis in trauma patients.

Study design

Patients that are 18 years or older and suffered trauma can be included in the study. Blood will be sampled at time-points:
- MMT (Sampled by MMT helicopter team, if applicable)
- SEH (Sampled at time of admission at the emergency department)
- Day 1 after trauma
- Day 3 after trauma
- Day 5 after trauma
- Day 7 after trauma
- Day 10 after trauma
- Day 14 after trauma

When possible, an existent arterial line or intravenous line will be used to sample blood. A venapuncture will only be performed when necessary. Informed consent will be asked if a venapuncture is necessary to obtain blood.

Study burden and risks

The only intervention in this study is the sampling of blood. No risks are associated.
The patients in this study have suffered serious injury. In most cases, the patient will be sedated during the first days after admission to the hospital. The burden of the study will be neglectable in these patients, because blood can be drawn from the arterial or venous line so no vena puncture will be necessary. This research may be considered group-related, since scientific knowledge on the immunological reactions in trauma patients can only be obtained by studying this specific group of patients.

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

Patients admitted to the UMC St Radboud with trauma

Exclusion criteria

Age below 18,
expected clinical risks of blood sampling,
known HIV/AIDS,
conditions known to influence the immune response (e.g. auto-immune diseases),
use of medication known to influence the immune response (e.g. steroids)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending

Start date (anticipated):	01-10-2011
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO Date:	07-12-2011
Application type:	First submission
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	NL38169.091.11