Neuropathological changes in the Wall of the large Bowel of Patients with functional Bowel Disorders

STUDY PROTOCOL

Study Protocol Version 1; 2018-10-18

Study protocol

To investigate neurohistomorphological changes of the colon and rectal wall and their genesis in patients with a bowel evacuation disorder in the sense of an intestinal transit and expulsion disorder.

Short title of the study:

Neuropathological achanges of the intestinal wall in patients with bowel evacuation disorder.

Head of the clinical trial:

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Summary:

Constipation and defecation disorders affect about 15% of the European population and of those up to 30% of the patients over 65 years of age. For those affected, this is associated with major restrictions in quality of life and high health care costs .
The underlying causes of constipation and defecation are complex and onlypartially understood.

Intestinal (full wall) resections taken in clinical practice from these patients when conservative therapy has been exhausted show rarefaction of ganglion cell nests in the myenteric plexus and submucosal plexus as well as changes in cholinergic innervation [Han EC et al 2012, Bassotti G. et al 2007, Wedel T. et al 2002].

Initial histopathological investigations suggest an inflammatory genesis of this rarefaction of ganglion cell nests, which will be further characterised/investigated in the context of this study on the basis of further histopathological and serological investigations. This may lead to novel therapeutic approaches that can causally treat the symptoms of those affected.

Introduction:

Intestinal transit disorders (constipation/obstipation) and/or defecation disorders (expulsion disorders) are widespread symptoms in our culture, which, depending on their severity, can become a disease. Epidemiological studies showthat up to 30% of the population over the age of 65 is affected. The suffering of those affected is usually very high.

The patients are usually treated conservatively at first. The focus is on lifestyle changes, dietary adjustments and medication to support bowel movements. If the symptoms persist despite consistent conservative therapy, additional diagnostics such as laboratory tests, sonography and colonoscopy are performed.
Further diagnostic steps include anal manometry, defecography and colon transittime.

In individual cases, bowel wall biopsies are taken as a further specific diagnostic tool, for example before a sacral nerve pacemaker (SNS= sacral neurostimulation)is indicated. In a study by Valli et al. it was shown that full-wall biopsies can be taken without significant risks for the patients and are very helpful for differentiated diagnosis [Valli PV et al. 2018]. In other cases, bowel resection is necessary due to mechanically induced causes of bowel dysfunction.

From 2015 onwards, the systematic neuropathological examination of whole-wall samples was performed on the bowel specimen of patients who were surgically treated in our clinic for defecation disorders. In addition, in individual cases in which no bowel resection was indicated, rectal full-wall samples were taken to confirm the diagnosis and indication for SNS and examined neuropathologically in the same way. The intestinal wall was examined for ganglion cell nests in the myenteric plexus and the submucosal plexus in order to identify the pathophysiological cause of the transport disorder.

In addition to the described rarefaction of the ganglion cell nests in the myenteric plexus and the submucosal plexus, initial results show both a change in the cholinergic innervation and changes that suggest a postinfectious reaction. Increasing evidence links gastroenteritic germs with chronic intestinal motility disorders [Porter CK et al. 2013, Mearin F et al. 2009], so that a Campylobacter or Yersinia infection could well be the trigger for the observed neuropathological changes. Should such an infection be diagnosed in our patient population, antibiotic treatment in the early stages of the disease could possibly prevent the neuropathological changes described.

The aim of the study:

The aim of the study is to illuminate the pathomechanism of chronic intestinal emptying disorders. In addition to the identification of histopathological features on intestinal wall specimen, possible causes are to be clarified on the basis of serological investigations. If the further investigations confirm our hypothesis, novel therapeutic/preventive approaches could be generated.

Type of trial, study design/methodology:

Clinical observational study, prospective

Method:

Currently, patients found to have rarefaction of ganglion cell nests in the myenteric and submucosal plexus in whole wall specimens receive prokinetics (e.g. Resolor) or sacral neurostimulation if conservative therapy is exhausted. Those in whom this therapy fails and/or in whom bowel evacuation can be attributed to morphological changes of the bowel such as massive kinking or stenosis in the imaging programs performed (MR defecography, colon KE, CT if necessary, colon transit time measurement (Hinton test)) are candidates for bowel resection.

The following additional steps are to be taken to carry out the planned studies:

- The intestinal preparations (n=58) already taken for diagnostic purposes (rectal full-wall biopsy) or in the course of an intestinal resection on the patient's own specimen and the future specimens are to be preserved and examined in detail histopathologically and, if necessary, molecularly pathogenetically.

- In addition, EDTA blood (10ml) should be taken and stored anonymously at -20 degrees Celsius for later serological examinations for a maximum of 10 years.

- Furthermore, the clinical data will be completed with the help of a systematic questioning of the patients beyond the scope of a medical history. In addition, scores regarding their health and psychological well-being (PHQ-9), quality of life (SF-36) and their bowel habits (Wexnerscore and Longoscore) are collected.

The neuropathological examinations planned within the framework of this study will be carried out at the Institute for Neuropathology of the University of

Cologne, Josef-Stelzmann-Str., 50931 Cologne. Blood samples for obtaining EDTA serum will be taken during the follow-up examination at the Evangelisches Klinikum Köln Weyertal (EVK), Weyertal 76, 50931 Cologne. The EDTA serum is centrifuged at the Institute of Neuropathology of the University of Cologne, Josef-Stelzmann-Str., 50931 Cologne, stored and examined in the laboratory there.

The sample preservation of the intestinal wall for the extended neuropathological and molecular pathological processing, the clinical follow-up examinations (questioning and scores) as well as the blood samples (optional) are only taken within the framework of this study after prior information and written consent of the patient.

Patient numbers:

58 so far (ongoing study)

Inclusion criterion:

Patients with severe defecation disorders, both in terms of colonic transit disorder and obstructive defecation disorder, and combinations of both, who have been managed conservatively and require a full-wall bowel biopsy or bowel resection for medical indication.

Exclusion criteria:

Lack of consent

Ethical conduct of the clinical trial:

The present study protocol was written in accordance with the Declaration of Helsinki in the currently valid version.
These principles include, but are not limited to, ethics committee procedures, patient education and informed consent, protocol adherence, administrative documents, data collection, patient record (source documents).
A patient may only be enrolled in the study if he or she has given consent to do so after being informed orally and in writing by an investigator about the nature, significance and scope of the study in an appropriate and comprehensible manner. It must be clear to him/her that he/she can withdraw his/her consent at any time and without giving reasons, without incurring any disadvantages. The original of the written consent is kept in the study folder of the study centre. The patient will be given a copy of the written informed consent form. In addition, a copy of both documents will be enclosed in the patient's file.

Patient information and consent form as well as all other documents received bythe participants will be submitted to the responsible ethics committee for approval before use. Within the framework of monitoring, it is checked whether the respective current consent was signed by the patient concerned.

Data protection:

The provisions of the data protection laws are observed. It is ensured that all research materials and data are adequately pseudo-anonymized in accordance with data protection regulations prior to scientific utilization. People who do notconsent to the disclosure will not be included in the study.

Literature:

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