Joint outcome of prophylactic treatment of haemophilia in Sweden evaluated by Magnetic Resonance Imaging (MRI)

Research group

Rolf Ljung, MD, PhD, Professor of Paediatrics, Lund University, Dept. of Paediatrics, Paediatric Clinic Malmö-Lund, Skåne University Hospital, SE 20502 Malmö, Sweden. Principal investigator clinical issues.

Björn Lundin, MD, PhD, Senior Consultant, Dept for Medical Imaging and Physiology, Skåne University Hospital Lund, SE 22185 Lund, Sweden. Principal investigator MRI issues.

Pia Petrini, MD, Senior Consultant, Paediatric Department of Coagulation Disorders, Karolinska University Hospital, SE-17176 Stockholm, Sweden

Gunilla Müller, MD, Senior Consultant, Dept of Radiology, Skåne University Hospital Malmö, SE 20502 Malmö, Sweden

Veli Söderlund, MD, PhD, Senior Consultant, Department of Radiology, Karolinska University Hospital, 17176 Solna, Sweden

Fariba Baghaei. MD, PhD, Senior Consultant, Coagulation Centre, Sahlgrenska University Hospital, 41345 Göteborg, Sweden

General aim

The general aim of this project is to improve prophylactic treatment of hemophilia by evaluation of joint status.

Specific aims

- To determine, by use of MRI, the joint outcome of prophylactic treatment using the Swedish model

  To study the evolution on MRI of joint changes by age in young individuals with severe and moderate haemophilia

- To determine the joint outcome in patients with moderate hemophilia treated without prophylaxis in comparison to age-matched patients with severe hemophilia on prophylaxis

- To study the correlation of the MRI score and the physical ‘Hemophilia Health Joint Score’ and the number of joint bleeds.
To study the value of MRI scoring for assessment of the severity of joint changes in hemophiliacs.

**Background and introduction**

Sweden is the foremost pioneer when it comes to prophylactic treatment of haemophilia (Nilsson et al 1992). The Swedish patient population is unique and is being prospectively followed and evaluated. Factor concentrates for haemophilia treatment are very expensive and there is a need for comparative (cost-benefit and cost-effectiveness) evaluations of haemophilia treatment. Our group (BL;RL) has developed a new MRI-based scoring system for haemophilia arthropathy (Lundin et al. 2004) that in collaboration with an international research group has been modified (Lundin et al. 2005) and validated (Doria et al. 2006).

Subclinical bleedings have been suggested to be of importance for developing haemophilic arthropathy (Petterson et al. 1980, Soreff & Blombäck 1980, Löfqvist et al 1997, Lundin et al 2005, Manco-Johnson et al. 2007). MRI of joints in children offers the possibility of early detection of subtle changes in the soft tissues in the joint after bleeds. No larger studies are on record to correlate MRI-findings with function. Children with severe haemophilia have been shown to have an excellent joint outcome as adults if treated on a prophylactic regimen. It may be questioned if we under-treat some children in particular with moderate haemophilia, who are not on prophylactic treatment, resulting in joint disease in early adulthood that could have been prevented.

Conventional radiography (X-ray) is the present gold standard for structural assessment of haemophilic arthropathy, and the X-ray classification method recommended by the World Federation of Hemophilia (WFH) is the Pettersson score (Pettersson et al. 1980). Outcome measures by means of X-ray score have been helpful for evaluating haemophilia care over the last decades. However, X-ray primarily visualizes bone, but is less efficient for analysis of soft tissues. Thus, initial and more subtle changes associated with haemophilic arthropathy, such as minor synovial hypertrophy and small hemosiderin deposits as well as cartilage defects not causing joint space narrowing, are not detected. Modern haemophilia treatment aims at prevention and early arrest of arthropathy, and, subsequently, there is need to visualize and assess slight changes that are not divulged by X-ray images.

Magnetic resonance imaging (MRI) is an imaging modality which provides tomographic images with high soft-tissue contrast in any plane. In joints of haemophiliacs, MRI detects the earliest alterations including haemarthros, effusion, synovial hypertrophy, haemosiderin depositions as well as minor cartilage defects without joint space narrowing, and MRI can enable detailed evaluation of progression of the arthropathic changes.

We have designed and presented a sensitive MR scoring method for detailed evaluation of single joints which separates reversible and irreversible joint changes (Lundin et al. 2004). In attempt to further develop and standardize MRI scoring methods for evaluation of hemophilic arthropathy, we have in international cooperation together with Canadian and American researchers presented (Lundin et al 2005) and evaluated (Doria et al 2006) a comprehensive MRI scoring system including both a rough score for simple evaluation of multiple joints and a more extensive score for detailed evaluation of single joints, and we are currently engaged
in further international work with the aim to fuse the previous scales into one single and
general basic MRI score for haemophilic arthropathy (accepted ISTH Congress 2011). This
refined scale will be used in this study.

Study design

This is an observational, descriptive outcome study. The primary outcome measure is the
MRI-score (four joints, (anes, knees) and worst joint), and the secondary outcome measure
is the physical haemophilia joint score. Determinants are mode of treatment, age, number of
joint haemorrhages and physical activity. Participating centers: Three treatment centers,
Malmö, Stockholm and Göteborg, and 2 MRI departments (Malmö, Stockholm).

Study group

Every patient in Sweden who is born between 1980 and 1999 and has severe or moderate
hemophilia A or B will be offered to participate (approximately 120 patients) at the time of a
scheduled visit to the hemophilia clinic. It is a realistic goal to be able to include 80-100.

Methods

Medical records.
Medical data on individuals will be collected from the medical files and the haemophilia
registry at the Malmö Centre for Thrombosis and Haemostasis which contains the data needed
in this study, i.e number of joint bleeds and joint and annual physical orthopaedic score.

HAL (Haemophilia Activity List)
This is a disease self-administered specific, validated tool to measure activity. Patients will be
asked to fill in a short questionnaire (Van Genderen et al. 2004).

MR-protocol.
For each patient, four joints (both knees and both ankles) are investigated at one occasion. In
order to achieve standardized measurements, both centres will use MRI Scanners with same
field strength and apply a uniform MRI protocol comprising the same type and number of
sequences. No contrast agent is administered. The investigation time for all four joints is
maximum 90 minutes.

Image analysis.
Three independent musculoskeletal radiologists evaluate the MR-images of each joint (triple
read) according to a specified scoring system. The three radiologists individual readings
(scores) will be compared and analysed for reader agreement, and a final MR-score for each
joint will be extracted by means of a majority procedure.
Statistical methods

Statistical support: Susanne Stjernqvist, RSKC (Region Skånes Kompetens Centrum), Lund

When studying the association between the MRI score and the age we use a Jonckheere-Terpstra test. We assume a significance level of 0.05, and that the study contains 80 persons in ages between 12 and 31 years (4 persons at each age). Further on we assume the mean MRI score to be 1 among 12-year-olds and that it increases linearly to 4 among 31-year-olds. Using these assumptions the power of finding a significant increase is above 80% which is a standard level.

We compare patients who received prophylactic treatment with patients who have not received this treatment by counting the number of patients with a MRI score above and below zero for each group. The results are presented in a cross table.

For evaluating the relations between different procedures we perform pair wise comparisons using the spearman correlation. The relations we are interested in are between MRI score and physical score, MRI score and the number of bleedings, and finally the physical score and the number of bleedings.

Budget plan

Grants

Previous grants available for this project 20,000 €
Application has been made to and positive preliminary answers received from pharmaceutical companies for an unrestricted grant.

Costs

MRI, evaluation and scoring of MRI from 80 patients at a cost of 10,000 SEK/patient = 800,000 SEK
Research time approx. 250,000 SEK
Overhead approx. 20%, 200,000 SEK
Unforeseen costs + misc. 100,000 SEK
Total budget: 1,350,000 SEK

Working plan

Recruitment will start 2011 and MRI will normally be offered at the annual visit at the Haemophilia Centre. It will take approximately 1½-2 years to collect the material and ½ year to evaluate and present the results.
Preliminary results

The MRI procedure used in this study has been applied in other studies and proved to be feasible. The MRI-scoring system to be used has been validated and published in its original versions and will first half 2011 be submitted in a refined simplified version.

Significance

Haemophilia treatment is extremely expensive due to the cost of concentrates. Evaluation using MRI adds a new, sensitive instrument for optimising treatment in the individual patient. The Swedish model, often referred as ‘golden standard’ will be evaluated.

MRI may reveal early changes in joints that may cause morbidity later in life and may justify therapeutic intervention.

The study will provide valuable experiences on optimal protocol design for cost-effective evaluation of haemophilia joints by MRI

Ethics and disclosures

The study has been submitted to the Regional Ethical Committee (Regionala Etikprövningsnämnden i Lund).

The present research program is initiated by the investigators and will be partly sponsored by unrestricted grants from several pharmaceutical industries without any possibility to influence design or evaluation.

RL (principal investigator clinical issues) is a member of Bayer’s International Hemophilia Advisory Board and is frequently invited to talk at scientific (not commercial) symposia sponsored by Bayer, Baxter, Octapharma, NovoNordisk and Biovitrum. This consultancy function has no association or conflict of interest to the present project.

BL (principal investigator MRI issues) has been invited to talk at scientific (not commercial) symposia sponsored by Bayer and Baxter and is a radiologic consultant evaluating MRI in different international studies. This consultancy function has no association or conflict of interest to the present project.

PP, GM, VS and FB have no reported conflicts of interest in this project.
References


Van Genderen et al., *Haemophilia activities list (HAL)*, Haemophilia 2004, 10, 565).