Søknad om prosjektmidler fra NKSD for 2017

Long-term outcomes in individuals with disorders of sex development (DSD): a 15-year follow-up of somatic and mental health, psychosocial and psychosexual outcomes and health-related quality of life.

Sammendrag

Prosjektet er en oppfølgingsstudie av pasienter med medfødt usikker somatisk kjønnsutvikling, disorders of sex development (DSD), tidligere beskrevet som "intersex" tilstander. Dette er en medfødt tilstand der kjønnet ikke kan fastsettes umiddelbart etter fødsel. Dette er en søknad om tilskudd for oppstart av prosjektet der pasientene som ble inkludert i 2002-2004 blir rekontaktet og bedt om å delta i en oppfølgingsstudie. Vi vil analysere allerede rapporterte og innsamlede data fra første inkluderingstidspunkt fra journal, semi-strukturerte intervjuer og validerte spørreskjemaer for å få en evaluering av somatisk og psykisk helse, psykososiale fungering og psykoseksuell utvikling samt livskvalitet. Disse bakgrunnsdataene, samt et nytt informert samtykke fra pasientene vil styrke en søknad om en PhD eller postdoktorstipend til Helse Sør-Øst Norge RHF eller Forskningsrådet på sikt. Prosjektet vil bedre grunnlaget for vurdering av dagens behandling og dermed forebygge mentale, psykososiale og psykoseksuelle vansker. Et uttalt mål i regjeringens handlingsplan mot diskriminering på grunn av seksuell orientering, kjønnsidentitet og kjønnsuttrykk 2017-2020, er utvikling av forskningsbasert kunnskap om personer født med somatisk usikkert kjønn. Denne oppfølgingsstudien av pasienter med DSD er nettopp en slik etterspurt studie. Prosjektet vil styrke samarbeidet mellom kompetansetjenesten Senter for sjeldne diagnoser (SSD) og behandlingstjenesten for DSD på Oslo universitetssykehus, og samtidig er god brukermedvirkning ivaretatt gjennom SSDs kontakter. Ingen norsk studie av denne pasientgruppen har så langt blitt publisert, og Norge er ikke medlem av allerede eksisterende internasjonale DSD nettverk. Et nært samarbeid i denne studien med erfarne og kjente internasjonale forskere innenfor DSD-feltet fra Institutt for kvinner- og barns helse, Karolinska Universitetssykehus i Sverige, som allerede er medlem av DSD nettverket, DSD-LIFE, et Europeiske Union rammeprogram, vil gi Norge en unik mulighet til å bygge nettverk med andre tverrfaglige team i fremtiden ved å benytte de samme standardiserte prosedyrene i denne studien.

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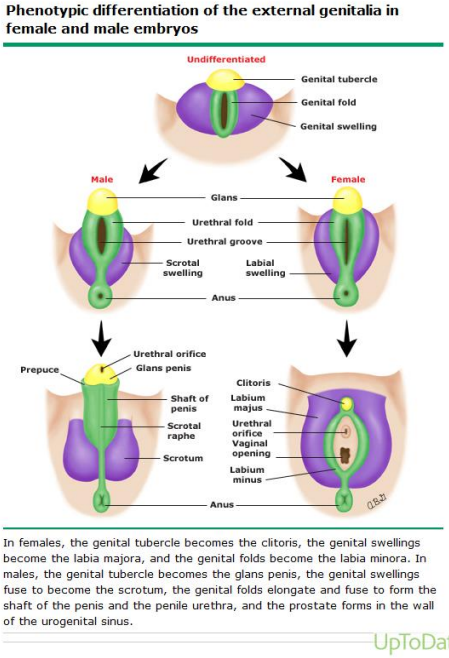
1. PROJECT TITLE

Long-term outcomes in individuals with disorders of sex development: a 15-year follow-up of health, psychosexual outcomes and quality of life.

Project leader (PI): Anne Wæhre, phD

2.INTRODUCTION AND BACKGROUND

Disorders or differences of sex development (DSD), formerly described as intersex conditions, are congenital conditions in which development of the chromosomal, gonadal, or anatomic sex is atypical [1]. DSDs with genital abnormalities occur in approximately one in 1000 to 4500 live births [2]. In 2006, a consensus statement was produced concerning the management of DSD [1]. In Norway there are two medical centers with multi-disciplinary teams experienced in such conditions, at the Children's departments of Oslo and Haukeland University Hospital, giving this care for children up to the age of 18 years.



Many publications in the last decades have reported the distress of adult individuals with DSD [2,3]. The overall goal for the treatment and care for patients with DSD is good quality of life (QoL), but current knowledge concerning the psychosocial situation and health related QoL (HRQoL) is limited and show controversial results. In some studies the general QoL is good [4,5], other studies find impaired QoL and distress [6-8], and one large Swedish epidemiological study show less optimal psychosocial situation for one of the diagnostic groups [9].

This is an application for a startup project where the patients included in 2002-2004 will be contacted and asked to participate in the follow-up study (see work package 1 Figure 5). We will analyze already reported and collected data at inclusion time from the medical journal, semi structured interviews and validated questionnaires to get an evaluation of somatic and mental health, psychosocial and psychosexual outcomes, and HRQoL. This background data and a new informed concent from the patients will strengthen an application for a phD or Postdoctoral fellowship to The South-Eastern Norway Regional Health Authority or The Research Concil of Norway in a longer perspective.

2.1. Needs description

In the Government's action plan against discrimination based on sexual orientation, gender identity and gender expression 2017-2020, "Security, diversity, openness" [10] it is written that "to date the intersex group have remained virtually invisible to the public. It is therefore important to get a better knowledge base about intersex, including the group's need for health care services." One aim outlined in the action plan is to develop research-based knowledge about the situation of persons born with DSD, where one particularly wants qualitative studies of living conditions and challenges. This project will just be such a sought-after research.

No Norwegian study of this patient group has so far been published, and Norway is not member of already existing international DSD networks. A close collaboration in this study with experienced and well-known international scientists within the DSD field from Department of Women's and Children's Health, Karolinska University Hospital in Sweden, who already are a member of the DSD network, the dsd-LIFE project, a European Union Framework Programme, will give Norway a unique opportunity to network with other multidisciplinary teams in the future by collecting the same standard operating procedures within this study.

3. HYPOTESIS, AIMS AND OBJECTIVES

The overall aim of the study is to evaluate medical, surgical, psychosocial and psychosexual outcomes and HQoL in individuals with DSD, with specific focus on outcomes concerning psychosexual development from child to adult, and patient and parent reported experience of the clinical care.

To study this, we will:

(i) Evaluate somatic and mental health, psychosocial and psychosexual outcomes, and HRQoL in individuals with DSD divided in three age groups at inclusion time in 2002-2004; newborns, 1-7 years and 12-18 years, and the comparison and control groups and their parents, and the same outcomes identified in a long-term follow-up now 15 years later.

(ii) To improve clinical care in general, and secure the transition to adult care the last aim of the project is to collect both patient and parent related outcome measures (PROM) and patient and parents related experience measures (PREM) of the clinical care in general, and particularly the medical treatment.

4. PROJECT METHOLOGY

4.1 Project arrangements, method selection and analyses

Recruitment took place at Oslo University Hospital, Rikshospitalet between 2002 and 2004. The sample consisted of 30 newborns admitted to the hospital in this period of time because of uncertain sex and genital anomalies, and 30 patients in each age-group, 1-7 years and 12-18 years, already enrolled in the multi-disciplinary DSD team. Also included in the study was an age-matched comparison group with another congenital disorder; bladder exstrophy/ epispadias, and a control group of healthy siblings.

Methods:

Genetic testing in the follow-up study: will be offered to the patients with an unclear specific diagnosis of DSD in collaboration with Professor Agneta Nordenström Department of Women's and Children's Health, Karolinska Institutet, Sweden and Professor Arvid Heiberg at the Department of Genetics at Oslo University Hospital.

Mental health of the adolescents and adults for the follow-up study will be assessed by Child Assessment Schedule (CAS)[11], Child Behavior Checklist (CBCL)[12] and the General Health Questionnaire (GHQ-30) [13]for the adult patients.

Health-Related Quality of life for the children, adolescents, adults and parents in the follow-up study will be assessed by Pediatric Quality of Life (PedsQL)[14], and the Quality of Life Scale (QOLS)[15] for adults and parents.

Gender role and gender identity at long-term follow-up: Gender identity and dysphoria will be assessed in the follow-up study with the Utrecht Gender Dysphoria Scale (UGDS)[16] and Body Image Questionnaire [17] from the age of 16 years.

DSD Study Questionnaires for the follow-up study: To ensure patients related outcome measurements, we have developed a questionnaires ("DSD questionnaire"). The questionnaire

could be completed at home or at the study center by the patients themselves depending on the preferences of the participants.
For patients aged 13-18 there will be questions ("DSD Questionnaire 13-18 years of age") about sexual functionality and satisfaction, sexual orientation and gender identity included in the semi structured interview (CAS).
Sexual function will also be assessed with the Female Sexual Function Index (FSFI) [18], and the Sexual Health Inventory for men (SHIM) [19] from the age of 18 years.
Treatment Satisfaction will also be assessed by a patients reported experience measures questionnaire ("PREM Questionnaire") from the age of 16 years. The questionnaire could be completed at home or at the study center by the patients themselves. This questionnaire is anonymous.
Statistical methods: to ensure the use of appropriate statistical methods for the data analysis we have a close collaboration with Manuela Zucknick, PhD, Associate professor, at Oslo Center for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo.

4.2 Participants, organization and collaborations

Professor Dr.Med.Trond Diseth (TD) will be the overall leader of all subprojects. Professor Diseth is head of the Division of Child and Adolescent Psychiatry at OUS-Rikshospitalet and has during the last 20 years led and contributed with child and adolecents psychiatry research across disciplines in cooperation with child surgeons and pediatricians. Medical doctor, PhD Anne Wæhre (AW), specialist in pediatrics and in training to be a child-and adolescent psychiatrist will be engaged in the current project through her position at Center for Rare Disorders who is the national competence center for patients with DSD. In addition, the project is based on interdisciplinary collaboration with key academic/scientific personnel that includes *(i) Department of Child Surgery at OUS, Senior consultant Trine Sæther Hagen (TSH), (ii) Department of Paediatric and Adolescents Medicine, Senior consultant Anne Grethe Myhre (AGM), (iii) Department of Genetics, Prof. dr.med. Arvid Heiberg (AH), (iv) Department of urology, Senior consultant Alexander Schultz (AS), (v) Department of gynaecology, Senior consultant Kirsten Hald (KH), (vi) Department of endocrology, Senior consultant Johan Arild Evang (JAH), (vii) head of Center for Rare Disorders, Olve Moldestad OM). All at Oslo University Hospital. To ensure close collaboration with the other DSD team in Norway, the project is based on collaboration with Prof. dr.med Helge Ræder Department of Pediatrics, Haukeland University Hospital, Bergen have been involved in the project planning and will implicate the same standard operating procedures.* ***In relation to the present project, our international collaborators are of particular importance and some part of the project will be performed in Agneta Nordenström and Louise Frisén groups who both have an impressive record in relation to studies in DSD.*** *(x) Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden, Professor Agneta Nordenskjöld (AN),(xi) Child and Adolescent Psychiatry Research Center and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, Senior Consultant Louise Frisèn (LF).*

See Figure 5 for detailed project management and resources

4.4 Plan for activities, visibility and dissemination

Milestones

Task	Milestones	2017	2018	2019	Key partners
WP1	Evaluation already included data (somatic and mental health, psychosocial, psychosexual outcomes, and HRQoL) of DSD patients **included in 2002-2004**; newborns, 1-7 years and 12-18 years, and their parents, and the comparison and control groups.	→ ★			TD, AW, AGM, AH, TSH, LF
WP2	Re-contact and evaluation (somatic and mental health, psychosocial, psychosexual outcomes, and HRQoL) of the same patients and the comparison and control groups from WP1: **15 years later**; now aged 13-15 years, 16-22 years and 27-33 years.		→ ★		TD, AW, AGM KH, JAE, AN TSH, AS, LF
WP3	The patients,and the comparison and control groups and parents will at the timepoint 15 years after first inclusion be asked to complete a specific PROM questionnaire on issues concerning sexual health, gender identity and surgery. Validated questionnaires on gender identity and sexual health will be asked to complete.		↗ ★ ↘		TD, AW
WP4	The patients and the comparison group. and parents will also be asked to complete a PREM questionnaire on the patients and parents experience of the clinical care.				

Figure 5. Project managing and resources during 3 years study period. The persons involved in the different WPs are indicated to the right. The red stars denote expected publications from the project. Prof. Diseth (TD) will be the overall leader of all subprojects. New PhD or post-doc student will work on WP1-4, and AW will work on WP1 in this start-up project.

Disseminations

The aim of the present project is to substantially advance our understanding of DSD with the ambition to improve quality of life in a lifelong perspective. Recipients of the insights obtained will be the scientific community where the results will be presented at scientific meetings. In addition, and of equal importance will be presentation of the results obtained to a broader public, by popular presentation in newspapers, television, web pages and blogs.

4.5 Plan for implementation

Integration of new knowledge into the management and treatment of patients with DSD is a key goal of the project. The current project can lead to new insight regarding the indication and timing of genital surgery, as well as patients and parents own outcome measures and experiences on clinical concerns and care. These will enable us to have a broader understanding of the patient population and the medical service quality as we implicate this new knowledge in the multidisciplinary team at both OUS-Rikshospitalet and Haukeland University Hospital in approximately 2020.

5. USER INVOLVEMENT

We are incessantly trying to involve patients and patient-organizations in our research. This means a “bidirectional interaction”. The Centre for Rare Disorders is a key partner in this project through medical doctor, phD Anne Wæhre employed at the Center who has planned the study together with Professor Diseth in the Child and Adolescent Psychiatry Division at Oslo University Hospital. The Center has already established a close collaboration with the CAH society; “Norsk Forening for CAH [www.cah.no]” in Norway led by Mrs. Margrethe Tangre. This user-organization is actively involved and partner in the project as CAH represents one of the most common diagnosis in the study population. Through The Center for

Rare Disorders members from the CAH society as well as other patients with a DSD diagnosis connected to the Center have been involved in development and evaluation of the "DSD questionnaire" to ensure appropriate questions. On regular basis, we will present our recent research advantage on the CAH society meetings. This axis will be further developed in the coming years by regular meeting with the organization and in blogs, where two-ways communications is stressed. We will also shortly have a web page where our project are presented with the possibility for patients with DSD diagnosis to communicate with the researchers and other involved health personnel. In this ways, a broader patient-group could contribute to recruitment and study design in coming studies and shed light on the health problems that need particular attention in relation to new treatment option and care.

6. ETHICS

The first inclusions of patients are approved by the Regional Ethical Committee and conducted according to the Declaration of Helsinki (*Ref.nr S-02252*). An application for the follow-up study is submitted to Regional Ethical Committee the 14th of June 2016, and will be discussed at the next meeting the 25th of August (*Ref. nr.: 2016/1186 A*). Informed consent from parents in the original study in 2002-2004 was obtained. A new informed consent from the parents to participants now under 16 years of age will be obtained, as for participants above 16 years of age.

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