ESMI

European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative

Study Protocol
ESMI Prospective Cohort

JPND research

EU Joint Programme – Neurodegenerative Disease Research

European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative (ESMI)

Protocol ESMI Prospective Cohort

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Background

ESMI is a European multicentre research project that has the principle goal to facilitate and prepare clinical trials in SCA3/MJD. To achieve this goal, four work packages (WP) were defined that have the following, specific objectives:

- to set up the world´s largest cohort of SCA3 mutation carriers by bringing together and enlarging existing SCA3 cohorts (WP 1),
- to develop a model of disease evolution in SCA3 that conceives the preclinical (pre-ataxia) stage and the ataxia stage as the graded manifestation of one disease process (WP 1),
- to develop new functional tests based on movement recording that complement clinical scales and can detect and quantify subtle coordination deficits (WP 2),
- to study effects of lifestyle and gender on disease evolution (WP 2),
- to develop easily extractable MRI markers that indicate brain pathology before onset of clinically manifest ataxia and reflect disease progression (WP 3),
- to develop new biochemical disease and progression markers based on RNA profiling and ataxin-3 measurement (WP 4).

Setting up the ESMI prospective cohort (WP 1) is a core activity of the ESMI project that has the purpose to reach the goals of the other WPs, in particular to validate new functional tests based on movement recording (WP 2), and to develop new MRI and biochemical biomarkers (WP 3, WP 4).

Study design

Prospective, multicentre observational study of SCA3/MJD mutation carriers

Study objectives

The primary objective of the ESMI Prospective Cohort is to acquire longitudinal clinical data of SCA3/MJD mutations carriers together with movement recording data, standardized MRIs and biomaterials.

Study population

The study population consists of

- SCA3/MJD mutation carriers (presymptomatic and symptomatic)
- persons at risk (1st degree relatives of SCA3/MJD patients) with a 50% risk to carry the SCA3/MJD mutation who have not been diagnostically tested, and who do not wish to be tested
- controls (including spouses (family controls), unrelated persons (community controls), and persons at risk who were negatively tested)

The study population includes subjects who had previously participated in the EUROSCA or RISCA cohort and newly recruited participants. Mutation carriers are recruited from the whole spectrum of disease severity including non-ataxic subjects with a focus on preclinical and mildly ataxic subjects.

Persons at risk are recruited according to the RISCA protocol. Thus, diagnostic genetic testing is offered, but not required. In those who do not wish diagnostic genetic testing, the genetic tests are performed anonymously.

Assessment

Assessment is done according to the attached CRF. The used instruments are the following:

Scale for the assessment and rating of ataxia (SARA)

To assess the presence and severity of ataxia, the newly developed SARA scale is used. SARA is based on a semi-quantitative assessment of cerebellar ataxia on an impairment level. SARA underwent a rigorous validation procedure involving three clinical trials in large groups of SCA and non-SCA ataxia patients, and controls. By correlating SARA ratings with global assessment of ataxia it was shown that SARA measures ataxia linearly over a wide range of disease severity (Schmitz-Hübsch *et al.* 2006).

Spinocerebellar ataxia functional index (SCAFI)

To assess the severity of ataxia in an objective way, three quantitative tests, 8m timed walk (gait), PATA rate (speech) and 9 hole pegboard test (hand function) are applied. Together, these tests yield the SCAFI which is a validated and sensitive measure of ataxia (Schmitz-Hübsch *et al.* 2008a).

Composite cerebellar functional severity score (CCFS)

To assess the hand function of the dominant hand a combined score using the 9 hole pegboard and two mechanical click devices that are placed in a predefined distance are used. The CCFS is a validated tool that is accurate in measuring the severity of ataxia focussing on the dominant hand (du Montcel *et al.* 2008).

Inventory of non-ataxia signs (INAS)

To assess non-ataxia symptoms, INAS is used. INAS consists of a clinical part which is based on a standard neurological examination and a history part which is based on an interview. The history part covers a wide range of symptoms that may occur in association with degenerative ataxias (Schmitz-Hübsch *et al.* 2008b).

Friedreich´s ataxia rating scale (FARS) – Activities of daily living (ADL)
To assess the ability to perform essential daily activities (e.g. speech, cutting food, dressing and personal hygiene), the basic ADL part of the FARS is used. Impairments in these activities of daily living are of crucial importance in terms of quality of life as well as necessary nursing care (Subramony *et al.* 2005)

EQ-5D

Health related Quality of life is assessed using EQ-5D, a generic instrument that has been developed and validated by the EuroQuol Group (1990) and is available in validated translations for use as a questionnaire.

PHQ-9

Assessment of depressive symptoms is done using a validated 9-item short form of the Patient Health Questionnaire (PHQ), a questionnaire that has been developed to screen for psychiatric co-morbidity in unselected populations (Spitzer *et al.* 1999).

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is used as a sensitive tool to screen for cognitive impairment (Nasreddine *et al.* 2005).

Lifestyle assessment

A detailed questionnaire is completed on every visit to access different aspects of potentially disease modifying lifestyle factors. On the one hand, lifestyle factors like smoking and alcohol consumption are assessed. On the other hand, we ask for physical activity in subjects' everyday life (active vs. sedentary lifestyle) and specific physical exercises for ameliorating ataxia.

Movement and activity recording

Movement and activity recording are performed according to the attached protocol. A detailed motor assessment with quantitative recording is acquired by using the MultiKinect motion capture system with six preinstalled cameras. Physical activity recording is recorded using the ActivPal® accelerometers. Different feature of gait, like step length and step time as well as intra-limb coordination, have been shown to be altered in ataxic patients. Motor tasks with increasing complexity (stance, walk, tandem etc.) are performed to detect subtle motor changes (Ilg *et al.* 2007, Ilg *et al.* 2009).

Magnetic resonance imaging (MRI)

MRIs are performed according to the attached protocol. Regularly phantom scans are acquired for quality assurance. MRI are centrally analzyed in Bonn (Germany).

Biosampling

Biosampling is done according the attached protocol. Samples are stored locally except Aachen and Essen who send their samples for storage to Bonn. Shipping to Bonn is done following the respective DZNE protocol.

Follow-up visits

Follow-up visits are done annually.

Participation

All study sites do the clinical assessment and biosampling. Only selected sites participate in the MRI and movement/physical activity recording study (see Table 1).

Table 1	Clinical Assessment	Biosampling	MRI	MultiKinect/ ActivPAL®
Bonn	✓	✓	✓	✓
London	✓	✓	✓	
Azores	✓	✓		
Coimbra	✓	✓		
Tübingen	✓	✓		✓
Nijmegen	✓	✓	✓	✓
Aachen	✓	✓	✓	
Essen	✓	✓	✓	
Heidelberg	✓	✓	✓	
Santander	✓	✓		
Groningen	✓	✓	✓	

Attachment:

- ESMI Prospective Cohort CRF
- ESMI Biosampling Manual
- ESMI MRI Manual
- ESMI Movement Recording Manual

References

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