our study is part of the multicentre study "e-OPMD": bringing focus to OPDM research in Europe. "Pathophysiology and therapeutic approaches in Oculopharyngeal Muscular Dystrophy (OPMD)"

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON35337

Source
ToetsingOnline

Brief title
e-OPMD

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym
muscular dystrophy of among other the eye- and swallowing-muscles, oculopharyngeal muscular dystrophy (OPMD)

Research involving
Human

Sponsors and support

Primary sponsor: L'Association Française contre les Myopathies (en Centre national de la recherche scientifique)
Source(s) of monetary or material Support: L'Association Française contre les Myopathies (en Centre national de la recherche scientifique)

Intervention

Keyword: Dutch OPMD population, Oculopharyngeal Muscular Dystrophy, Pathophysiology, Therapeutic approaches

Outcome measures

Primary outcome

Outcome measures of our part of the study are:

- Identification of deregulated pathways by OPMD onset by transcriptome

analysis on the biopsies from presymptomatic OPMD patients.

- Identification of deregulated pathways involved in disease progression.

- Identification of deregulated pathways involved in the specific distribution

of muscleweakness in OPMD.

- Correlation of histological and clinical data of Dutch OPMD patients

Secondary outcome

The clinical and demographical characteristics like age, sex, body weight,

length, age at onset, first complaint at onset, disease severity, co-morbidity

and blood parameters (CK, ASAT, ALAT and LDH)

Study description

Background summary

Oculopharyngeal mucular dystrophy (OPMD) an autosomal dominant, late onset (>40yrs), muscular dystrophy which is clinically characterized by progressive ptosis, dysphagia and limb-girdle muscle weakness. OPMD is a rare disease (1:100000) with a worldwide distribution. In some ethnical groups the incidence is higher like the French Canadians in Quebec and the Bukhara Jews in Israel. OPMD is caused by a GCG-repeat expansion in the genes encoding the poly(A)binding protein nuclear 1 (PABPN1). This GCG repeat encoding an alanine tract expansion at the N-terminus of the protein. The mutant form of PABPN1 contains 12-17 alanines, while 10 alanines are present in the normal protein. Intranuclear inclusions (INI*s) in muscle fibers are a pathological hallmark of OPMD. Despite the fact that the genetic cause of OPMD is known, little is known about the molecular mechanisms leading to INI*s and muscle dysfunction and the reason why the mutation only affects specific muscle groups. Like other proteinopathies, or diseases that are associated with the formation of protein-aggregated in affected tissues, such as Huntington*s, there is no pharmacological treatment for this disease. Recent data suggest that these intranuclear inclusions contain mutant insoluble PABPN1 molecule (Calado et al. 2000) as well as ubiquitin (= a regulatory protein which tags broken proteins to degrade them via the ubiquitine-proteasome system, UPS) and the subunits of the proteasome (=large protein complex which degrades proteins). The current view is to explain these results is that the polyalanine expansios in PABPN1 confer a toxic "gain-of-function" to the protein, and induce misfolding and aggregation to PABPN1 inclusions, which are then targeted to the ubiquitin-proteasome degradation pathway (Calado et al 2000). But recent data suggest that the ubiquitin-proteasome system itself seems to be the predominant deregulated pathway in OPMD patients (Anvar et al 2011). Anvar 2011 found that exression of expPABPN1 leads to down-regulation of proteasome-encoding genes. In turn, proteasome down-regulation during muscle aging triggers expPABPN1 accumulation and accumulation of exp PABPN1 leads to extensive proteasome down-regulation. This feed forward model could justify the appearance of INI*s in specific muscles and the late onset of the disease. Recent data suggest that, in myotubes of OPMD mice, the ratio of soluble/insoluble expPABPN1 is significantly lower compared with that of the non-mutated (wildtype) protein. This suggests that the difference in soluble/insoluble ratio of expPABPN1 can contribute to muscle weakness in OPMD (raz et al Am J Pathol. 2011 Aug 17.)
The primary function of PABPN1 is nuclear polyadenylation, an mRNA processing reaction leading to the formation of the poly(A) tail at the end of mRNA's (Wahle 1991). In agreement with this, decrease PABPN1 levels in vivo in drosophila and mouse myoblasts leads to shortened mRNA poly(A)tails (Benoit et al 2005, Apponi et al. 2010). Consistent with this function, several lines of evidence suggest that the involvement of mRNA metabolism in OPMD pathogenesis. Recent data have also implicated apoptosis in OPMD pathogenesis (Chartier et al 2006, Davies et al. 2008).
The aim of this European consortium is to decipher the molecular mechanisms involved in OPMD pathogenesis in order to base innovative therapeutic strategies based on. The strengths of this consortium are the utilization of different animal-models (mouse and Drosophila), each having a specific

advantage, as well as patient biopsies, and the variety and complementarity of techniques and approaches utilized in the different laboratories of the network.
Within this network a genetically tractable OPMD model has been generated, using Drosophila- PABPN1 with a polyalanine extansion of different lengths. Studies with this model have shown that although the polyalanine expansion is required for the disease, the context of the disease is also essential. A mouse model has been generated by expressing alanine-expanded PABPN1 specifically in skeletal muscle. Recent detailed phenotypic characterization of this model mouse model in combination with transcriptome studies by members if this consortium revealed progressive deregulation of the muscle atrophy network with progressive muscle atrophy restricted to fast glycolytic fibres (Trollet et al 2010). Biopsies from OPMD patients are also available in this consortium. New biopsies will have to be collected. This will allow us to study human muscle cells from affected as well as unaffected muscles in different stages of the disease.
Finally, therapeutic tools and strategies have been developed previously, by participants in this consortium. An antibody against PABPN1 has been identified (Verheesen et al. 2006), which, when expressed intracellular in Drosophila muscles, completely prevents OPMD symptoms, thus revealing its high therapeutic potential (Chartier et al 2009).
Significant understanding of pathological mechanisms and consequent evidence-based therapeutic approaches in rare diseases are severely hampered by the difficulty in generating sufficiently large patient data sets and limited availability of relevant bio-resources. In order to overcome this, our eOPMD network combines clinical and basic research with the focus to understand the pathophysiology of this rare muscular dystrophy and to design new therapeutic approaches. Central to our research is the hypothesis that important pathogenic pathways in OPMD are shared between diseased tissue and different cellular and animal model systems.

The teams involved in present network are as follows, each of them having their unique expertise:
Partner 1: Dr. Martine Simonelig . Institut de genetique Humaine UPR 1142 CNRS. France.
Partner 2: Dr. Vered Raz. Leiden University medical Centre- Human genetics.
Partner 3: Dr. Gillian Butler-Browne. Institut de myologie UMRS 974. France.
Partner 4: Prof. George Dickson. Royal Holloway- University of London. UK.
Partner 5. Prof. Dr. Baziel van Engelen. Radboud university Nijmegen Medical centre. Dept. Neurology.

Our contribution to this study will be:
- Repeating musclebiopsies from the same Dutch OPMD patients who were biopsied previously, in 2003 (protocolnumber d.d. 12-06-2002, CMO-nr: 2002/108).
- Muscle biopsies will also be taken from all newly diagnosed patients, known in our centre.
- Muscle biopsies will also be taken from the adult offspring of the newly

diagnosed OPMD patients.

All biopsies will be taken from a clinically often affected muscle (quadriceps) as well as a muscle which is often clinically unaffected (tibialis anterior). This material will be subjected to transcriptome analysis, in order to
- Identify pathways involved in disease progression. By subjecting the first (2003) and second (2011) quadriceps biopsy to transcriptome analysis, we will investigate pathways involved in the disease progressiveness with reduced inter-individual-variation noise.
- Identify pathways involved in the specific distribution of muscleweakness in OPMD. By subjecting the clinically affected (quadriceps) muscle and the clinically unaffected muscle (tibialis anterior) to comparative transcriptome analysis, we will identify the molecular basis behind OPMD muscle group specificity, with reduced inter-individual-variation noise.
- Identify deregulated pathways involved in disease onset. By subjecting the muscle biopsies from the presymptomatic OPMD patients (that means the adult offspring of an OPMD patient that carries the mutation but is not clinically affected, yet) to transcriptome analysis and comparing them to the biopsies from OPMD patients and comparing the quadriceps muscle to the tibialis anterior muscle within the same presymptomatic individual, we will identify deregulated pathways involved in disease onset. See flowchart 2 on p. 22 of the protocol.

Furthermore we will take questionnaires from all the symptomatic OPMD patients, concerning onset, course, current symptoms and impact of the disease. We will subject all the participants to a standardized neurological exam including a muscle power measurement using the handheld dynamometer and a venipuncture in order to perform DNA analysis (if not performd before) and laboratory values (CK, ASAT, ALAT and LDH) in order to correlate clinical, histological and genetic aspects in the Dutch OPMD population, which is never described to this extend.
Within our study we contribute to OPMD research twofold:
By contributing to this multicentre study we help in clearing up pathophysiology of OPMD. On the other hand we describe the Dutch OPMD population.
These results, combined with the results from the animal models within this eOPMD project, will be used as a basis for future clinical trials with gene- and pharmacological therapies.

Study objective

Within this complete European consortium animal models as well as patient material are utilized, in order to uncover the pathogenic pathways in OPMD that are at the centre of the disease, eventually in order to design rational evidence based therapeutic strategies for this largely neglected muscular dystrophy.
We utilize different animal models (each having their advantage) as well as patient material and a variety of genetic and molecular techniques and

approaches utilized in the different laboratories in our network. This will allow us to:
A. Identify cellular pathways underlying OPMD pathology.
B. Validate information obtained in animal models (e.g. through genetic approaches) up to patient material.
C. rapidly test therapeutic approaches and identify those with the highest therapeutic potential.
The research is based on the hypothesis that important pathogenic pathways in OPMD are shared between diseased tissue and different cellular and animal model systems. Combining the advantages of cross-species transcriptome analysis, fast and efficient genetic and suppressor screens in Drosophila, function studies in mice and validation in human cells and tissues, we aim to uncover those pathogenic pathways in OPMD that are at the centre of the disease with the objective to design rational evidence-Based therapeutic strategies for this largely neglected muscular dystrophy.

The objectives of this complete research are divided among the 5 partners:
Aim1: (partner 1 and 3) Identification of the molecular pathways involved in OPMD through genetic screens using the drosophila model.
Aim2: (responsible partner 2, participant partners 1-5) understanding the mechanisms underlying the pathophysiology of OPMD by
a.)Identification of OPMD deregulated pathways by trans-model transcriptome analysis.
b.) Validation of OPMD deregulated pathways in the mouse model and on human biopsies.
c.) Functional validation of the biological pathways deregulated in OPMD using the drosophila model
d.) Identification of OPMD deregulated pathways by transcriptome and proteome analysis
e.) Correlating the clinical and the histological pathways in OPMD patients.
Aim3: (responsible partner 3, participant partners 3, 4) Development of gene strategies for OPMD.
Aim4: (Responsible partner 4, participant partners 1, 4) Pharmacological approach to treat OPMD.

The aims specific for our centre will be:
A. contributing to this multicentre research by taking two muscle biopsies from Dutch OPMD patients and their adult offspring. With the sub-objectives:
I. Identify pathways involved in disease progression. By subjecting the first (2003) and second (2011) quadriceps biopsy to transcriptome analysis.
II. Identify pathways involved in the specific distribution of muscleweakness in OPMD. By subjecting the clinically affected (quadriceps) muscle and the clinically unaffected muscle (tibialis anterior) to comparative transcriptome analysis.
III. Identify deregulated pathways involved in disease onset. By subjecting the muscle biopsies from the presymptomatic OPMD patients (that means the adult offspring of an OPMD patient that carries the mutation but is not clinically

affected, yet) to transcriptome analysis and comparing them to the biopsies from OPMD patients and comparing the quadriceps muscle to the tibialis anterior muscle within the same presymptomatic individual.
B. Correlating clinical, histological and genetic characteristics of Dutch OPMD patients

Study design

- We have a database with all the OPMD patients known in our clinic since 2003. We will send all these patients information concerning this study and ask them whether they want to participate.
- From the patients on this list, we know whom participated in the preceding study (Protocolnr: d.d. 12-06-2002, CMO-nr: 2002/108). We will only contact the adult offspring from the OPMD patients who did not participate in the preceding study, in order to send them information about this study and ask whether they want to participate
- As soon as the informed consents are returned, we will send the questionnaires to the symptomatic OPMD patients and we will make an appointment for the examinations with all the participants.
- On the planned day we will perform on all the participants: a short medical history and
- a neurological exam including a muscle power measurement, using the hand held dynamometer.
- a venipuncture will be performed to screen DNA for the OPMD specific mutation (if not performed before) and to assess for parameters of muscle injury (CK, ASAT, ALAT, LDH)
- a needle muscle biopsy of 2 muscles (m. quadriceps and m. tibialis anterior) will be performed.

- transcriptome analyses on de cells from the muscle biopsies will be performed by partner 2, LUMC
- histological analysis will be performed in our centre.
- We will correlate clinical, histological and genetic data of the complete Dutch OPMD population.

Study burden and risks

For this project the participants have to travel once to the Radboud University medical Centre Nijmegen. The examinations are planned on 1 part of the day. The only burden for the participants is the time they have to make. The biopsy and the blood collection are no additional risks for the 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

- Age between 18-80 years
- Phenotype of autosomal OPMD. This phenotype inlcudes a positive family history with involvement of two or more generations.
-The presence of ptosis (defined as either vertical separation of at least one palpebral fissure that measures less than 8 mm at rest) OR previous corrective surgery for ptosis
-The presence of dysphagia, defined as swallowing time greater than seven seconds when drinking 80 mL of ice-cold water
- Or confirmd OPMD by a 12-17 alanin trinucleotide repeat of the PABPN1 gene.
- Or adult offspring of a newly diagnosed OPMD patient (and thus did not participate in the 2003 study)

Exclusion criteria

- serious external ophtalmoplegia before the age of 60
- presence of myotonia
- comorbidity affecting muscle dysfunction
- abnormal bleeding

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-02-2012
Enrollment:	66
Type:	Actual

Ethics review

Approved WMO

Date:	27-12-2011
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	NL38086.091.11