Neuromuscular Transmission in Amyotrophic Lateral Sclerosis (NETALS)

This study is currently recruiting participants.
Verified by Assistance Publique - Hôpitaux de Paris, December 2009

First Received: February 11, 2009   Last Updated: April 29, 2010   History of Changes

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>Assistance Publique - Hôpitaux de Paris</th>
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<tbody>
<tr>
<td>Collaborators:</td>
<td>Association pour la Recherche sur la Scérose Latérale Amyotrophique Association Française contre les Myopathies (AFM), Paris</td>
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<td>Information provided by:</td>
<td>Assistance Publique - Hôpitaux de Paris</td>
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<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT00847847</td>
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**Purpose**

Consistent data suggest that neuromuscular transmission is impaired in ALS patients. Neuromuscular junctions dysfunction may appear very early in the disease, as shown by data in animal models. The pathogenesis of this neuromuscular transmission impairment is unknown. Nogo A isoform, a possible marker of the disease over-expressed in skeletal muscle of ALS patients, can be involved. We will characterize the pathophysiological mechanisms implicated using a complete study of the structure and function of the NMJ on muscle biopsies, in a group of 20 ALS patients compared to 10 controls.

<table>
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<th>Condition</th>
<th>Intervention</th>
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<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Procedure: Anconeus Muscle biopsy</td>
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</table>

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Control: Uncontrolled
Intervention Model: Parallel Assignment
Masking: Open Label

Official Title: Neuromuscular Transmission in Amyotrophic Lateral Sclerosis

Resource links provided by NLM:

- Genetics Home Reference related topics: amyotrophic lateral sclerosis
- MedlinePlus related topics: Amyotrophic Lateral Sclerosis
Further study details as provided by Assistance Publique - Hôpitaux de Paris:

Primary Outcome Measures:

- Characterization of the neuromuscular transmission dysfunction in ALS by studying the structural and functional features of NMJs on muscle biopsies [ Time Frame: within the 15 days after inclusion (month 0 = M0) ] [ Designated as safety issue: No ]

Secondary Outcome Measures:

- Search for correlations between the results of the structural and functional study of neuromuscular junctions on muscle biopsy and surface-EMG and clinical data [ Time Frame: at M0, M3, M6 ] [ Designated as safety issue: No ]

Estimated Enrollment: 30  
Study Start Date: March 2009  
Estimated Study Completion Date: August 2011  
Estimated Primary Completion Date: August 2011 (Final data collection date for primary outcome measure)

<table>
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<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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</table>
| 2    | control subjects with muscle biopsy | Procedure: Anconeus Muscle biopsy  
Anconeus muscle specimens will be surgically removed. The biopsy will be performed under regional anaesthesia and will require an about 5 cm incision of the skin and muscle fascia from the lateral condyle to over the ridge of the proximal ulna, 3 or 4 cm distal to the tip of the olecranon. A triangular muscle flap will be removed, and then the fascia and skin will be closed with running dissolving suture. |
| 1    | ALS patients with muscle biopsy | Procedure: Anconeus Muscle biopsy  
Anconeus muscle specimens will be surgically removed. The biopsy will be performed under regional anaesthesia and will require an about 5 cm incision of the skin and muscle fascia from the lateral condyle to over the ridge of the proximal ulna, 3 or 4 cm distal to the tip of the olecranon. A triangular muscle flap will be removed, and then the fascia and skin will be closed with running dissolving suture. |

Detailed Description:

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder involving motor neurons of the motor cortex, brain stem and spinal cord. Its pathogenesis remains unknown, and the only drug currently available, riluzole, only modestly prolongs survival. Consistent data show that neuromuscular transmission is impaired in patients with ALS. The significance of these abnormalities remains unknown, but recent data suggest that they potentially play a key role in the pathogenesis of the disease. Neuromuscular junctions (NMJs) dysfunction may appear very early in the disease, as shown by data in animal models. The mechanisms of this neuromuscular transmission impairment are unknown. Nogo A belonging to the family of neurite outgrowth inhibitor proteins which is abnormally expressed in skeletal muscle of ALS patients, is probably involved as it has been shown that over-expression of Nogo A in wild-type muscle leads to destabilization of NMJs. A detailed study of the structure and function of the NMJ in ALS patient is mandatory to better characterize the pathophysiological mechanisms implicated.

The aim of this study is to characterize the neuromuscular transmission dysfunction in ALS. For this purpose, we will study the structural and functional features of NMJs on muscle biopsies in a group of 20 ALS patients compared to 10 controls. Using biopsies of a vestigial muscle, the
anconeus, we will perform a morphological study of the NMJ, including routine histochemistry, immunohistochemical studies for NMJ major proteins and immune IgG complexes and electron microscopy study. The number of acetylcholine receptors per endplate will be determined by radiolabeled alpha-bungarotoxin binding. Expression levels of Nogo-A will be determined in muscle specimens by western blot. Synaptic transmission at individual NMJs will also be studied ex vivo. We will record membrane potential over time using different nerve stimulation frequencies and we will analyze the properties of the miniature endplate potentials (spontaneous release of acetylcholine) and endplate potentials after stimulation of the nerve (evoked release of acetylcholine). The results of this structural and functional study of NMJ on muscle biopsy will be correlated with surface-EMG and clinical data.

This study will help identifying new mechanisms involved in the pathophysiology of ALS and potential new targets for future treatments.

Eligibility

Ages Eligible for Study: 18 Years to 75 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

1. ALS patients:
   - Inclusion criteria:
     - Aged 18 to 75 (inclusive)
     - Possible, probable (clinically or laboratory) or definite ALS according to the revised El Escorial criteria
     - Duration of the disease of less than 12 months
     - Willing and able to provide a written informed consent
     - With french social insurance affiliation
   - Exclusion criteria:
     - Cognitive changes or psychiatric condition, inability to give informed consent
     - Patient unable to contact or to be contacted by the investigator in case of emergency
     - Women who are pregnant or nursing
     - Concomitant medication contraindicating muscular biopsy (platelet suppressive agents if treatment can not medically be stopped 2 weeks before surgical procedure, oral anticoagulant therapy)
     - Medical condition contraindicating muscular biopsy (hypo-coagulative disease, allergy to anaesthetic drugs)
     - Medical condition susceptible to influence on EMG examination (concomitant neurological or rheumatological disease)

2. Controls:
   - Adult patients (minimum 18y) without neuromuscular disease
   - Undergoing elbow surgery for local joint or bone disease

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00847847

Contacts

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Locations

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Investigators
Principal Investigator: Gaelle Bruneteau, MD Assistance Publique - Hôpitaux de Paris

More Information

No publications provided

Responsible Party: Department Clinical Research (Yannick VACHER)
ClinicalTrials.gov Identifier: NCT00847847 History of Changes
Other Study ID Numbers: P080404
Study First Received: February 11, 2009
Last Updated: April 29, 2010
Health Authority: France: Ministry of Health

Keywords provided by Assistance Publique - Hôpitaux de Paris:
ALS Neuromuscular junction
Motor neuron Neuromuscular transmission
Pathophysiology Microelectrodes

Additional relevant MeSH terms:
Amyotrophic Lateral Sclerosis Nervous System Diseases
Sclerosis Neurodegenerative Diseases
Motor Neuron Disease Neuromuscular Diseases
Spinal Cord Diseases Pathologic Processes
Central Nervous System Diseases

ClinicalTrials.gov processed this record on August 05, 2010

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